CASE 4-18634

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

EV 786955766US — Express Mail Label Number

June 5, 2009 — Date of Deposit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE U.S. PATENT NO. 5,677,331

ISSUED: October 14, 1997

INVENTORS: Yiqing Zhou, Dianxi Ning, Shufen Wang, Deben Ding, Guofu Li, Chengqi Shan, and Guangyu Liu

FOR: ANTIMMALARIAL COMPOSITIONS

MS: Patent Ext.
Director for Patents
PO Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER FOR PATENT TERM EXTENSION APPLICATION

Sir:

Enclosed in triplicate is an application for the extension of U.S. Patent No. 5,677,331 under 35 U.S.C. §156.

The Director is hereby authorized to charge the Application Fee of $1,120.00 prescribed by 37 C.F.R. §1.20(j)(1), as well as any additional fees which may be required in connection with the filing of this Application for Patent Term Extension, to Applicant's Deposit Account No. 19-0134 in the name of Novartis. Two additional copies of this transmittal letter are being submitted for charging purposes.

Respectfully submitted,

Jennifer C. Chapman

Jennifer C. Chapman
Attorney for Applicant
Reg. No. 47,487

Novartis
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Date: June 4, 2009

CASE 4-18634

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

EV786955706645 (Express Mail Label Number)

June 5, 2009 (Date of Deposit)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE U.S. PATENT NO. 5,677,331

ISSUED: October 14, 1997

INVENTORS: Yiqing Zhou, Dianxi Ning, Shufen Wang, Deben Ding, Guofu Li, Chengqi Shan, and Guangyu Liu

FOR: ANTIMMALARIAL COMPOSITIONS

MS Patent Ext.
Director for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PATENT TERM EXTENSION APPLICATION UNDER 35 U.S.C.§156

Sir:

Pursuant to 35 U.S.C.§156 and 37 C.F.R.§1.710 *et seq.*, Novartis AG ("Applicant"), a Corporation organized under the laws of Switzerland, hereby requests an extension of the patent term due to regulatory review of U.S. Patent No. 5,677,331, which was granted on October 14, 1997.

Applicant asserts that it is the co-owner of the right, title and interest in U.S. Patent No. 5,677,331 by virtue of an assignment from the inventors Yiqing Zhou, Dianxi Ning, Shufen Wang, Deben Ding, Guofu Li, Chengqi Shan, and Guangyu Liu, to Ciba-Geigy AG (which later becomes part of Novartis AG through a merger) and Institute of Microbiology, Academy of Military Medical Sciences.

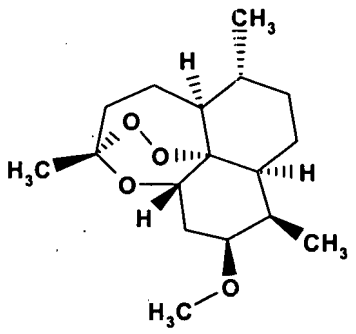
The assignment and the merger are recorded in the U.S. Patent and Trademark Office at Reel 008557, Frame 0400 on June 19, 1997 and Reel 011072, Frame 0019 on October 31, 2000, respectively.

Applicant asserts that the undersigned counsel, Jennifer C. Chapman, is authorized to act as its attorney in this matter.

In accordance with 35 U.S.C.§156 and 37 C.F.R.§1.740, Applicant provides the following information in support of its request for a patent term extension.

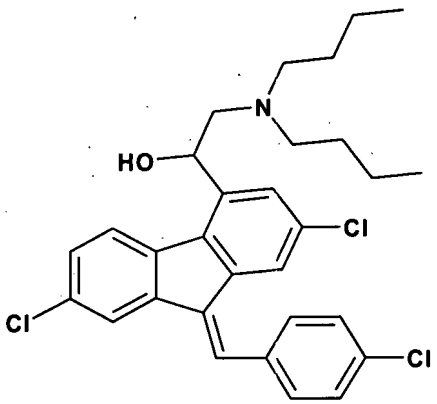
(1) Identification of the Approved Product

The approved product is Coartem®, which is a fixed combination of two antimalarial active ingredients: artemether and lumefantrine, having the chemical structure(s)



Artemether

and



Lumefantrine

respectively.

The chemical name of artemether is (3R,5aS,6R,8aS,9R,10S,12R,12aR)-decahydro-10-methoxy-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepine.

The chemical name of lumefantrine is (±)-2-dibutylamine-1-[2,7-dichloro-9-(4-chlorobenzylidene)-9H-fluorene-4-yl]ethanol.

The strength is 20mg/120mg, artemether / lumefantrine respectively.

The approved product is a tablet for oral administration.

The approved product is indicated for the treatment of acute, uncomplicated malaria infection due to *Plasmodium falciparum* in patients of 5 kg bodyweight and above.

A copy of the approved label for Coartem® is attached hereto as Appendix A.

2. **Identification of the Federal Statute under which Regulatory Review Occurred**

The approved product was subject to regulatory review under the Federal Food, Drug and Cosmetic Act, Section 505(b) (21 U.S.C.§355(b)).

3. **The Date of Permission for Commercial Marketing**

The approved product received permission for commercial marketing under Section 505(c) of the Federal Food, Drug and Cosmetic Act (21 U.S.C.§355(c)) on April 7, 2009. A copy of the FDA approval letter is attached hereto as Appendix B.

4. **Active Ingredient Statement**

There are two active ingredients in Coartem®: artemether and lumefantrine.

Neither artemether nor lumefantrine has been previously approved for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum Toxin Act prior to the approval of NDA 22-268 by the United States Food and Drug Administration on April 7, 2009.

5. **Statement of Timely Filing**

The last day on which this application could be submitted is June 6, 2009 which is 60 days after the approval of NDA 22-268 on April 7, 2009. This application is timely filed on or prior to June 6, 2009.

6. **Identification of Patent for which Extension is Sought**

This application seeks to extend the term of U.S. Patent No. 5,677,331, which issued October 14, 1997 to Yiqing Zhou, Dianxi Ning, Shufen Wang, Deben Ding, Guofu Li, Chengqi Shan, and Guangyu Liu, the term of which would otherwise expire on October 14, 2014.

7. **Patent Copy**

A complete copy of U.S. Patent No. 5,677,331, identified in paragraph 6 above, is attached as Appendix C.

8. Post-Issuance Activity Statement

No disclaimer, certification of correction, reexamination certificate or reissue has been filed, issued or requested with respect to U.S. Patent No. 5,677,331.

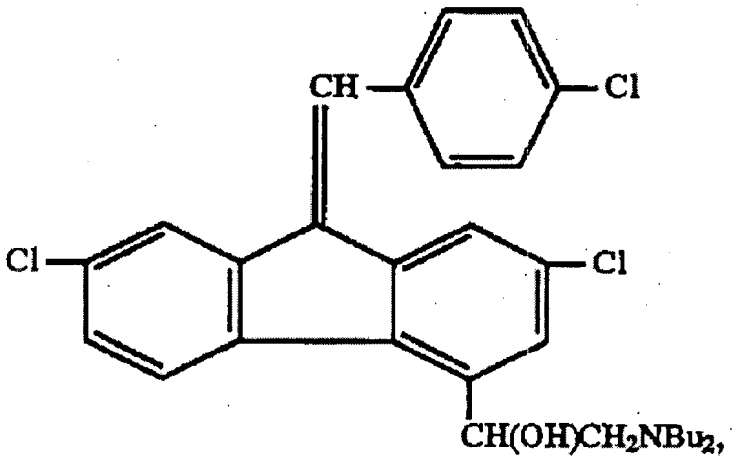
All maintenance fees have been timely paid. The 4th year maintenance fee was paid on April 2, 2001. The 8th year maintenance fee was paid on April 1, 2005. The 12th year maintenance fee was paid on March 18, 2009. Copies of the Maintenance Fee Statements are attached hereto as Appendix D.

9. Statement Showing How the Claims of the Patent for which Extension is Sought Cover the Approved Product

The claims of U.S. Patent No. 5,677,331 cover the approved product (claims 1-4), and a method of using the approved product (claim 5).

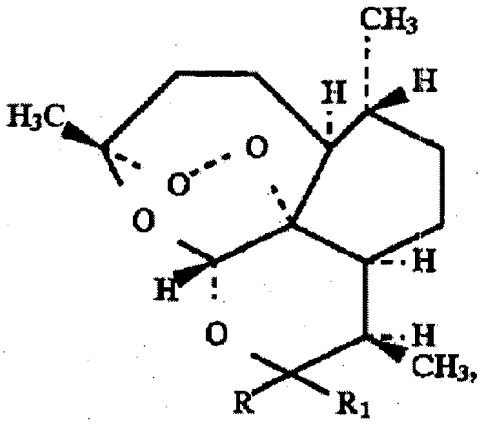
Claim 1 of U.S. Patent No. 5,677,331 reads as follows:

> 1. A pharmaceutical composition to be administered orally to humans, suitable for synergistic action of the combined active components against malaria, which composition consists of a synergistic antimalarially effective amount of a combination of the compound benflumetol of the formula:



(I)

in fixed combination with the compound artemether of the formula:



(II)

wherein one of R and R_1 individually represents methoxy, and the other represents hydrogen,

and pharmaceutically acceptable additives.

The approved product is a fixed combination of artemether (as in formulation (II) of claim 1 of U.S. Patent No. 5,677,331) and lumefantrine (as in formulation (I) of claim 1 of U.S. Patent No. 5,677,331). The approved product is an oral dosage form, and it is for the treatment of malaria. Hence, claim 1 covers the approved product.

Claim 2 of U.S. Patent No. 5,677,331 reads as follows:

2. A pharmaceutical composition according to claim 1, which composition consists of a synergistically effective amount of one to ten parts by weight of benflumetol (I) for each part by weight of artemether (II).

Coartem® tablets contain 20mg of artemether and 120mg of lumefantrine. The weight ratio of lumefantrine/artemether is 6, between 1 to 10 as required by claim 2. Hence claim 2 covers the approved product.

Claim 3 of U.S. Patent No. 5,677,331 reads as follows:

3. A pharmaceutical composition according to claim 1, which composition consists of a synergistically effective amount of three to seven parts by weight of benflumetol (I) for each part by weight of artemether (II).

Coartem® tablets contain 20mg of artemether and 120mg of lumefantrine. The weight ratio of lumefantrine/artemether is 6, between 3 to 7 as required by claim 3. Hence claim 3 covers the approved product.

Claim 4 of U.S. Patent No. 5,677,331 reads as follows:

> 4. A pharmaceutical composition according to claim 1 which composition consists of a synergistically effective amount of five to six parts by weight of benflumetol (I) for each part by weight of artemether (II).

Coartem® tablets contain 20mg of artemether and 120mg of lumefantrine. The weight ratio of lumefantrine/artemether is 6, between or equal to 5 to 6 as required by claim 3. Hence claim 3 covers the approved product.

Claim 5 of U.S. Patent No. 5,677,331 reads as follows:

> 5. A method of treating malaria which comprises administering orally to a human in need of such treatment a synergistic antimalarially effective amount of a combination of benflumetol of formula (I) and artemether of formula (II).

The approved product is indicated for the treatment of acute, uncomplicated malaria infection due to *Plasmodium falciparum* in patients of 5 kg bodyweight and above. Hence, claim 5 covers the method of using the approved product.

10. Statement of the Relevant Dates to Determine the Regulatory Review Period

The relevant dates and information pursuant to 35 U.S.C.§156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

The patent for which extension of the term thereof is sought claims a human drug product. The human drug product is a composition containing artemether and lumefantrine.

(A) No investigational new drug (IND) application was filed prior to the approval of the approved product. An IND was filed after the approval of the approved product in order to submit post-approval data. The IND number is 105,588.

(B) A New Drug Application (NDA) for Coartem® was received by the Department of Health and Human Services on June 27, 2008 and granted NDA No. 22-268.

(C) NDA No. 22-268 was approved on April 7, 2009.

11. Brief Description of Activities Undertaken During the Regulatory Review Period

As a brief description of the activities undertaken during the applicable regulatory review period, attached hereto as Appendix E is a chronology of the major communications between the U.S. Food and Drug Administration and the Applicant in NDA No. 22-268.

12. Opinion of Eligibility for Extension

Applicant is of the opinion that U.S. Patent No. 5,677,331 is eligible for extension under 35 U.S.C.§156 and 37 C.F.R.§1.720 because it satisfies all of the requirements for such extension as follows:

(a) 35 U.S.C.§156(a) and 37 C.F.R.§1.720(a)

U.S. Patent No. 5,677,331 claims a human drug product, a pharmaceutical composition containing fixed combination of two active ingredients artemether and lumefantrine.

MPEP 2751 states:

"A patent is considered to claim the product at least in those situations where the patent claims the active ingredient per se, or claims a composition or formulation which contains the active ingredient(s) and reads of the composition or formulation approved for commercial marketing or use"

(b) 35 U.S.C.§156(a)(1) and 37 C.F.R.§1.720(g)

The term of U.S. Patent No. 5,677,331 (expiring October 14, 2014) has not expired before the submission of this application.

(c) 35 U.S.C.§156(a)(2) and 37 C.F.R.§1.720(b)

The term of U.S. Patent No. 5,677,331 has never been extended.

(d) 35 U.S.C.§156(a)(3) and 37 C.F.R.§1.720(c)

The application for extension of the term of U.S. Patent No. 5,677,331 is submitted by the authorized attorney of the co-owner of record thereof in accordance with the requirements of 35 U.S.C.§156(d) and 37 C.F.R.§1.740.

(e) 35 U.S.C.§156(a)(4) and 37 C.F.R.§1.720(d)

The approved product, Coartem®, has been subjected to a regulatory review period before its commercial marketing or use.

(f) 35 U.S.C.§156(a)(5)(A) and 37 C.F.R.§1.720(h)

No other patent has been extended for the same regulatory review period for the approved product, Coartem®.

13. Length of extension claimed under 37 C.F.R.§1.740(a)(12)

The length of extension of the patent term of U.S. Patent No. 5,677,331 requested by Applicant is 284 days (till July 25, 2015) which length was calculated in accordance with 37 C.F.R.§1.775 as follows:

(a) The regulatory review period under 35 U.S.C.§156(g)(1)(B) began on June 27, 2008 (the effective date of the NDA) and ended on April 7, 2009 (the approval date), amounting to a total of 284 days which is the period of (i) and (ii) below:

(i) The period of review under35 U.S.C.§156(g)(1)(B)(i), the "Testing Period," which is 0 days;

(ii) The period of review under 35 U.S.C.§156(g)(1)(B)(ii), the "Application Period," began on June 27, 2008 and ended on April 7, 2009, which is 284 days;

(b) The regulatory review period upon which the period for extension is calculated is the entire regulatory review period as determined in subparagraph (13)(a) above (284 days) less:

(i) The number of days in the regulatory review period which were on or before the date on which the patent issued (October 14, 1997), i.e., 0 days, and

(ii) The number of days during which the Applicant did not act with due diligence, i.e., 0 days, and

(iii) One-half of the number of days remaining in the period in subparagraph (13)(a)(i) after subtracting the number of days in subparagraphs (13)(b)(i) and (13)(b)(ii), which is one-half of (0 - [0 + 0]) or 0 days;

which results in a period of 284-0=284 days.

(c) The number of days as determined in subparagraph (13)(b), when added to the original term (October 14, 2014), would result in the date of July 25, 2015.

(d) Fourteen (14) years when added to the date of the NDA Approval Letter (April 7, 2009) would result in the date of April 7, 2023.

(e) The earlier date as determined by subparagraphs (13)(c) and (13)(d) is July 25, 2015.

(f) Since the original patent was issued after September 24, 1984, the extension otherwise obtainable is limited to not more than five (5) years. Five years, when added to the original expiration of U.S. Patent No. 5,677,331 (October 14, 2014), results in the date October 14, 2019.

(g) The earlier date as determined in subparagraphs (13)(e) and (13)(f) is July 25, 2015.

14. Duty of Disclosure Acknowledgement Under 37 C.F.R.§1.740(a)(13)

Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

15. Fee Charge

The prescribed fee for receiving and acting upon this application is to be charged to Applicant's Deposit Account No. 19-0134 as authorized in the attached transmittal letter, submitted in triplicate.

16. Correspondence Address Required by 37 C.F.R.§1.740(a)(15)

All correspondence relating to this application for patent term extension should be addressed to:

Jennifer C. Chapman
Novartis
One Health Plaza, Bldg. 101
East Hanover, NJ 07936-1080

17. **Certification Under 37 C.F.R.§1.740(b)**

The undersigned hereby certifies that the instant application, including its attachments and supporting papers, is being submitted as one original and two copies thereof in accordance with 37 C.F.R.§1.740(b).

Respectfully submitted,

Novartis
Patents Pharma
One Health Plaza, Building 101
East Hanover, NJ 07936-1080

Jennifer C. Chapman
Attorney for Applicant
Reg. No. 47,487
(862) 778-1202

Date: June 4, 2009

Appendix A

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Coartem Tablets safely and effectively. See full prescribing information for Coartem Tablets.

Coartem (artemether/lumefantrine) Tablets
Initial U.S. Approval: 2009

----------INDICATIONS AND USAGE----------

- Coartem (artemether and lumefantrine) Tablets are indicated for treatment of acute, uncomplicated malaria infections due to *Plasmodium falciparum* in patients of 5 kg bodyweight and above (1)
- Coartem Tablets have been shown to be effective in geographical regions where resistance to chloroquine has been reported (1)
- Coartem Tablets should not be used to treat severe malaria or to prevent malaria (1)

---------DOSAGE AND ADMINISTRATION---------

- Coartem Tablets should be taken with food. (2.1, 5.2)
- Tablets may be crushed and mixed with one to two teaspoons of water immediately prior to administration to patients, including children (2.1)
- Coartem Tablets should be administered over 3-days for a total of 6 doses: an initial dose, second dose after 8 hours and then twice daily (morning and evening) for the following two days (2.2, 2.3)
- The adult dosage for patients with bodyweight of 35 kg and above is 4 tablets per dose for a total of 6 doses (2.2)
- The number of tablets per dose for children is determined by bodyweight, as shown in the chart below (2.3):

Tablets per dose by bodyweight; total of 6 doses over 3 days

5 to < 15 kg	1 tablet
15 to < 25 kg	2 tablets
25 to < 35 kg	3 tablets
35 kg and over	4 tablets

---------DOSAGE FORMS AND STRENGTHS---------

Tablets are scored and contain 20 mg artemether and 120 mg lumefantrine. (3)

----------CONTRAINDICATIONS----------

- Patients hypersensitive to artemether, lumefantrine, or to any of the excipients (4.1)

----------WARNINGS AND PRECAUTIONS----------

- Avoid use in patients with known QT prolongation, those with hypokalemia or hypomagnesemia, and those taking other drugs that prolong the QT interval (5.1, 12.5)
- Halofantrine and Coartem Tablets should not be administered within one month of each other due to potential additive effects on the QT interval. (5.1, 5.2, 12.3)
- Antimalarials should not be given concomitantly, unless there is no other treatment option, due to limited safety data. (5.2)
- QT prolonging drugs, including quinine and quinidine, should be used cautiously following Coartem Tablets; (5.1, 5.2, 7.6, 12.3)
- Substrates, inhibitors, or inducers of CYP3A4, including antiretroviral medications, should be used cautiously with Coartem Tablets, due to a potential loss of efficacy of the concomitant drug or additive QT prolongation (5.3, 7.1, 7.3)

----------ADVERSE REACTIONS----------

The most common adverse reactions in adults (> 30%) are headache, anorexia, dizziness, asthenia, arthralgia and myalgia. The most common adverse reactions in children (> 12%) are pyrexia, cough, vomiting, anorexia and headache. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- CYP3A4 Inhibitors: Use cautiously due to potential for QT prolongation (5.3, 7.1)
- Mefloquine: If used immediately before treatment, monitor for decreased efficacy of Coartem Tablets and encourage food consumption (2.1, 7.2)
- Hormonal Contraceptives: Effectiveness may be reduced; use an additional method of birth control (5.3, 7.3)
- Anti-Retrovirals: Use cautiously due to potential for QT prolongation, loss of anti-viral efficacy, or loss of antimalarial efficacy of Coartem Tablets (5.3, 7.3)
- CYP2D6 Substrates: Monitor for adverse reactions and potential QT prolongation (5.1, 5.4, 7.4)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may increase fetal loss. (8.1)
- Nursing Mothers: Use caution when administering to a nursing woman (8.3)
- Pediatric Use: Studied in children 2 months of age and older with a bodyweight of 5 kg and greater. (8.4)
- Geriatric Use: Not studied in geriatric patients (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 4/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Coartem (artemether/lumefantrine) Tablets are indicated for treatment of acute, uncomplicated malaria infections due to *Plasmodium falciparum* in patients of 5 kg bodyweight and above. Coartem Tablets have been shown to be effective in geographical regions where resistance to chloroquine has been reported [see *Clinical Studies (14.1)*].

Limitations of Use:

- Coartem Tablets are not approved for patients with severe or complicated *P. falciparum* malaria.
- Coartem Tablets are not approved for the prevention of malaria.

2 DOSAGE AND ADMINISTRATION

2.1 Administration Instructions

Coartem Tablets should be taken with food. Patients with acute malaria are frequently averse to food. Patients should be encouraged to resume normal eating as soon as food can be tolerated since this improves absorption of artemether and lumefantrine.

For patients who are unable to swallow the tablets such as infants and children, Coartem Tablets may be crushed and mixed with a small amount of water (one to two teaspoons) in a clean container for administration immediately prior to use. The container can be rinsed with more water and the contents swallowed by the patient. The crushed tablet preparation should be followed whenever possible by food/drink (e.g., milk, formula, pudding, broth, and porridge).

In the event of vomiting within 1 to 2 hours of administration, a repeat dose should be taken. If the repeat dose is vomited, the patient should be given an alternative antimalarial for treatment.

2.2 Dosage in Adult Patients (>16 years of age)

A 3-day treatment schedule with a total of 6 doses is recommended for adult patients with a bodyweight of 35 kg and above:

Four tablets as a single initial dose, 4 tablets again after 8 hours and then 4 tablets twice daily (morning and evening) for the following two days (total course of 24 tablets).

For patients weighing less than 35 kg, see Dosage in Pediatric Patients (2.3).

2.3 Dosage in Pediatric Patients

A 3-day treatment schedule with a total of 6 doses is recommended as below:

5 kg to less than 15 kg bodyweight: One tablet as an initial dose, 1 tablet again after 8 hours and then 1 tablet twice daily (morning and evening) for the following two days (total course of 6 tablets).

15 kg to less than 25 kg bodyweight: Two tablets as an initial dose, 2 tablets again after 8 hours and then 2 tablets twice daily (morning and evening) for the following two days (total course of 12 tablets).

25 kg to less than 35 kg bodyweight: Three tablets as an initial dose, 3 tablets again after 8 hours and then 3 tablets twice daily (morning and evening) for the following two days (total course of 18 tablets).

35 kg bodyweight and above: Four tablets as a single initial dose, 4 tablets again after 8 hours and then 4 tablets twice daily (morning and evening) for the following two days (total course of 24 tablets).

2.4 Dosage in Patients with Hepatic or Renal Impairment

No specific pharmacokinetic studies have been carried out in patients with hepatic or renal impairment. Most patients with acute malaria present with some degree of related hepatic and/or renal impairment. In clinical studies, the adverse event profile did not differ in patients with mild or moderate hepatic impairment compared to patients with normal hepatic function. No specific dose adjustments are needed for patients with mild or moderate hepatic impairment.

In clinical studies, the adverse event profile did not differ in patients with mild or moderate renal impairment compared to patients with normal renal function. There were few patients with severe renal impairment in clinical studies. No specific dose adjustments are needed for patients with mild to moderate renal impairment.

Caution should be exercised when administering Coartem Tablets in patients with severe hepatic or renal impairment [see *Warnings and Precautions (5.6)*].

3 DOSAGE FORMS AND STRENGTHS

Coartem Tablets contain 20 mg of artemether and 120 mg of lumefantrine. Coartem Tablets are supplied as yellow, round, flat tablets with beveled edges and scored on one side. Tablets are imprinted with N/C on one side and CG on the other side.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

- Patients hypersensitive to artemether, lumefantrine, or to any of the excipients of Coartem Tablets [see *Adverse Reactions (6.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Prolongation of the QT Interval

Some antimalarials (e.g., halofantrine, quinine, quinidine) including Coartem Tablets have been associated with prolongation of the QT interval on the electrocardiogram.

Coartem Tablets should be avoided in patients:

- with congenital prolongation of the QT interval (e.g., long QT syndrome) or any other clinical condition known to prolong the QTc interval such as patients with a history of symptomatic cardiac arrhythmias, with clinically relevant bradycardia or with severe cardiac disease.
- with a family history of congenital prolongation of the QT interval or sudden death.
- with known disturbances of electrolyte balance, e.g., hypokalemia or hypomagnesemia.
- receiving other medications that prolong the QT interval, such as class IA (quinidine, procainamide, disopyramide), or class III (amiodarone, sotalol) antiarrhythmic agents; antipsychotics (pimozide, ziprasidone); antidepressants; certain antibiotics (macrolide antibiotics, fluoroquinolone antibiotics, imidazole, and triazole antifungal agents); certain non-sedating antihistaminics (terfenadine, astemizole), or cisapride [see *Clinical Pharmacology (12.5)*].
- receiving medications that are metabolized by the cytochrome enzyme CYP2D6 which also have cardiac effects (e.g., flecainide, imipramine, amitriptyline, clomipramine) [see *Warnings and Precautions (5.4), Drug Interactions (7.4)* and *Clinical Pharmacology (12.3)*].

5.2 Use of QT Prolonging Drugs and Other Antimalarials

Halofantrine and Coartem Tablets should not be administered within one month of each other due to the long elimination half-life of lumefantrine (3-6 days) and potential additive effects on the QT interval [see *Warnings and Precautions (5.1),* and *Clinical Pharmacology (12.3)*].

Antimalarials should not be given concomitantly with Coartem Tablets, unless there is no other treatment option, due to limited safety data.

Drugs that prolong the QT interval, including antimalarials such as quinine and quinidine, should be used cautiously following Coartem Tablets, due to the long elimination half-life of lumefantrine (3-6 days) and the potential for additive effects on the QT interval. [see *Warnings and Precautions (5.1), Drug Interactions (7.5),* and *Clinical Pharmacology (12.3)*].

If mefloquine is administered immediately prior to Coartem Tablets there may be a decreased exposure to lumefantrine, possibly due to a mefloquine-induced decrease in bile production. Therefore, patients should be monitored for decreased efficacy and food consumption should be encouraged while taking Coartem Tablets [see *Dosage and Administration (2.1), Drug Interactions (7.2),* and *Clinical Pharmacology (12.3)*].

5.3 Drug Interactions with CYP3A4

When Coartem Tablets are co-administered with substrates of CYP3A4 it may result in decreased concentrations of the substrate and potential loss of substrate efficacy. When Coartem Tablets are co-administered with an inhibitor of CYP3A4, including grapefruit juice it may result in increased concentrations of artemether and/or lumefantrine and

potentiate QT prolongation. When Coartem Tablets are co-administered with inducers of CYP3A4 it may result in decreased concentrations of artemether and/or lumefantrine and loss of anti-malarial efficacy [see *Drug Interactions (7.1)*].

Drugs that have a mixed effect on CYP3A4, especially Anti-Retroviral drugs, and those that have an effect on the QT interval should be used with caution in patients taking Coartem Tablets [see *Drug Interactions (7.3)*].

Coartem Tablets may reduce the effectiveness of hormonal contraceptives. Therefore, patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control [see *Drug Interactions (7.3)*].

5.4 Drug Interactions with CYP2D6

Administration of Coartem Tablets with drugs that are metabolized by CYP2D6 may significantly increase plasma concentrations of the co-administered drug and increase the risk of adverse effects. Many of the drugs metabolized by CYP2D6 can prolong the QT interval and should not be administered with Coartem Tablets due to the potential additive effect on the QT interval (e.g., flecainide, imipramine, amitriptyline, clomipramine) [see *Warnings and Precautions (5.1), Drug Interactions (7.4)* and *Clinical Pharmacology (12.3)*].

5.5 Recrudescence

Food enhances absorption of artemether and lumefantrine following administration of Coartem Tablets. Patients who remain averse to food during treatment should be closely monitored as the risk of recrudescence may be greater [see *Dosage and Administration (2.1)*].

In the event of recrudescent *P. falciparum* infection after treatment with Coartem Tablets, patients should be treated with a different antimalarial drug.

5.6 Hepatic and Renal Impairment

Coartem Tablets have not been studied for efficacy and safety in patients with severe hepatic and/or renal impairment [see *Dosage and Administration (2.4)*].

5.7 *Plasmodium vivax* Infection

Coartem Tablets have been shown in limited data (43 patients) to be effective in treating the erythrocytic stage of *P. vivax* infection. However, relapsing malaria caused by *P. vivax* requires additional treatment with other antimalarial agents to achieve radical cure i.e., eradicate any hypnozoites forms that may remain dormant in the liver.

6 ADVERSE REACTIONS

6.1 Serious Adverse Reactions

The following serious and otherwise important adverse reactions are discussed in greater detail in other sections of labeling:

- Hypersensitivity Reactions [see *Contraindications (4.1)* and *Postmarketing Experience (6.3)*].

6.2 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rate observed in practice.

The data described below reflect exposure to a 6-dose regimen of Coartem Tablets in 1,979 patients including 647 adults (older than 16 years) and 1,332 children (16 years and younger). For the 6-dose regimen, Coartem Tablets was studied in active-controlled (366 patients) and non-controlled, open-label trials (1,613 patients). The 6-dose Coartem Tablets population was patients with malaria between ages 2 months and 71 years: 67% (1,332) were 16 years and younger and 33% (647) were older than 16 years. Males represented 73% and 53% of the adult and pediatric populations, respectively. The majority of adult patients were enrolled in studies in Thailand, while the majority of pediatric patients were enrolled in Africa.

Tables 1 and 2 show the most frequently reported adverse reactions (≥3%) in adults and children respectively who received the 6-dose regimen of Coartem Tablets. Adverse reactions collected in clinical trials included signs and symptoms at baseline but only treatment emergent adverse events, defined as events that appeared or worsened after the start of treatment, are presented below. In adults, the most frequently reported adverse reactions were headache, anorexia, dizziness, and asthenia. In children, the adverse reactions were pyrexia, cough, vomiting, anorexia, and headache. Most adverse reactions were mild, did not lead to discontinuation of study medication, and resolved.

In limited comparative studies, the adverse reaction profile of Coartem Tablets appeared similar to that of another antimalarial regimen.

Discontinuation of Coartem Tablets due to adverse drug reactions occurred in 1.1% of patients treated with the 6-dose regimen overall: 0.2% (1/647) in adults and 1.6% (21/1,332) in children.

Table 1: Adverse Reactions Occurring in 3% or More of Adult Patients Treated in Clinical Trials with the 6-dose Regimen of Coartem Tablets

System Organ Class	Preferred term	Adults* N=647 (%)
Nervous system disorders	Headache	360 (56)
	Dizziness	253 (39)
Metabolism and nutrition disorders	Anorexia	260 (40)
General disorders and administration site conditions	Asthenia	243 (38)
	Pyrexia	159 (25)
	Chills	147 (23)
	Fatigue	111 (17)

System Organ Class	Preferred term	Adults* N=647 (%)
	Malaise	20 (3)
Musculoskeletal and connective tissue disorders	Arthralgia	219 (34)
	Myalgia	206 (32)
Gastrointestinal disorders	Nausea	169 (26)
	Vomiting	113 (17)
	Abdominal pain	112 (17)
	Diarrhea	46 (7)
Psychiatric disorders	Sleep disorder	144 (22)
	Insomnia	32 (5)
Cardiac disorders	Palpitations	115 (18)
Hepatobiliary disorders	Hepatomegaly	59 (9)
Blood and lymphatic system disorders	Splenomegaly	57 (9)
	Anemia	23 (4)
Respiratory, thoracic and mediastinal disorders	Cough	37 (6)
Skin and subcutaneous tissue disorders	Pruritus	24 (4)
	Rash	21 (3)
Ear and labyrinth disorders	Vertigo	21 (3)
Infections and infestations	Malaria	18 (3)
	Nasopharyngitis	17 (3)

* Adult patients defined as >16 years of age

Table 2: Adverse Reactions Occurring in 3% or More of Pediatric Patients Treated in Clinical Trials with the 6-dose Regimen of Coartem Tablets

System organ class	Preferred Term	Children* N=1,332 (%)
General disorders and administration site conditions	Pyrexia	381 (29)
	Chills	72 (5)
	Asthenia	63 (5)
	Fatigue	46 (3)
Respiratory, thoracic and mediastinal disorders	Cough	302 (23)
Gastrointestinal disorders	Vomiting	242 (18)
	Abdominal pain	112 (8)
	Diarrhea	100 (8)

System organ class	Preferred Term	Children* N=1,332 (%)
	Nausea	61 (5)
Infections and infestations	Plasmodium falciparum infection	224 (17)
	Rhinitis	51 (4)
Metabolism and nutrition disorders	Anorexia	175 (13)
Nervous system disorders	Headache	168 (13)
	Dizziness	56 (4)
Blood and lymphatic system disorders	Splenomegaly	124 (9)
	Anemia	115 (9)
Hepatobiliary disorders	Hepatomegaly	75 (6)
Investigations	Aspartate aminotransferase increased	51 (4)
Musculoskeletal and connective tissue disorders	Arthralgia	39 (3)
	Myalgia	39 (3)
Skin and subcutaneous tissue disorders	Rash	38 (3)

* Children defined as patients ≤ 16 years of age

Clinically significant adverse reactions reported in adults and/or children treated with the 6-dose regimen of Coartem Tablets which occurred in clinical studies at < 3% regardless of causality are listed below:

Blood and lymphatic system disorders: eosinophilia

Ear and labyrinth disorders: tinnitus

Eye disorders: conjunctivitis

Gastrointestinal disorders: constipation, dyspepsia, dysphagia, peptic ulcer

General disorders: gait disturbance

Infections and infestations: abscess, acrodermatitis, bronchitis, ear infection, gastroenteritis, helminthic infection, hookworm infection, impetigo, influenza, lower respiratory tract infection, malaria, nasopharyngitis, oral herpes, pneumonia, respiratory tract infection, subcutaneous abscess, upper respiratory tract infection, urinary tract infection

Investigations: alanine aminotransferase increased, aspartate aminotransferase increased hematocrit decreased, lymphocyte morphology abnormal, platelet count decreased, platelet count increased, white blood cell count decreased, white blood cell count increased

Metabolism and nutrition disorders: hypokalemia

Musculoskeletal and connective tissue disorders: back pain

Nervous system disorders: ataxia, clonus, fine motor delay, hyperreflexia, hypoaesthesia, nystagmus, tremor

Psychiatric disorders: agitation, mood swings

Renal and urinary disorders: hematuria, proteinuria

Respiratory, thoracic and mediastinal disorders: asthma, pharyngo-laryngeal pain

Skin and subcutaneous tissue disorders: urticaria

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Coartem Tablets. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hypersensitivity including urticaria and angioedema. Serious skin reactions (bullous eruption) have been rarely reported.

7 DRUG INTERACTIONS

7.1 Ketoconazole

Concurrent oral administration of ketoconazole, a potent CYP3A4 inhibitor, with a single dose of Coartem Tablets resulted in a moderate increase in exposure to artemether, dihydroartemisinin (DHA, metabolite of artemether), and lumefantrine in a study of 15 healthy subjects. No dose adjustment of Coartem Tablets is necessary when administered with ketoconazole or other potent CYP3A4 inhibitors. However, due to the potential for increased concentrations of lumefantrine which could lead to QT prolongation, Coartem Tablets should be used cautiously with drugs that inhibit CYP3A4 [see *Warnings and Precautions (5.1, 5.3)*].

7.2 Prior Use of Mefloquine

Administration of three doses of mefloquine followed 12 hours later by a 6-dose regimen of Coartem Tablets in 14 healthy volunteers demonstrated no effect of mefloquine on plasma concentrations of artemether or the artemether/DHA ratio. However, exposure to lumefantrine was reduced, possibly due to lower absorption secondary to a mefloquine-induced decrease in bile production. Patients should be monitored for decreased efficacy and food consumption should be encouraged with administration of Coartem Tablets [see *Warnings and Precautions (5.2)* and *Clinical Pharmacology (12.3)*].

7.3 CYP3A4 Metabolism: Hormonal Contraceptives and Anti-Retroviral Drugs

Artemether induces CYP3A4 and both artemether and lumefantrine are metabolized primarily by CYP3A4.

Coartem Tablets may reduce the effectiveness of hormonal contraceptives. Therefore, patients using oral, transdermal patch, or other systemic hormonal contraceptives should

be advised to use an additional non-hormonal method of birth control [see *Warnings and Precautions (5.3)* and *Clinical Pharmacology (12.3)*].

Anti-Retroviral drugs (ARTs), such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors, are known to have variable patterns of inhibition, induction or competition for CYP3A4. No formal drug-drug interaction studies between Coartem Tablets and ARTs have been performed. However, Coartem Tablets should be used cautiously in patients on ARTs as the result may be an increase in lumefantrine concentrations causing QT prolongation or a decrease in concentrations of the ART resulting in loss of efficacy, or a decrease in artemether and/or lumefantrine concentrations resulting in loss of antimalarial efficacy of Coartem Tablets [see *Warnings and Precautions (5.3)* and *Clinical Pharmacology (12.3)*].

7.4 CYP2D6 Substrates

Lumefantrine inhibits CYP2D6 *in vitro*. Administration of Coartem Tablets with drugs that are metabolized by CYP2D6 may significantly increase plasma concentrations of the co-administered drug and increase the risk of adverse effects. Many of the drugs metabolized by CYP2D6 can prolong the QT interval and should not be administered with Coartem Tablets due to the potential additive effect on the QT interval (e.g., flecainide, imipramine, amitriptyline, clomipramine) [see *Warnings and Precautions (5.1, 5.4)* and *Clinical Pharmacology (12.3)*].

7.5 Sequential Use of Quinine

A single dose of intravenous quinine (10 mg/kg bodyweight) concurrent with the final dose of a 6-dose regimen of Coartem Tablets demonstrated no effect of intravenous quinine on the systemic exposure of DHA or lumefantrine. Quinine exposure was also not altered. Exposure to artemether was decreased. This decrease in artemether exposure is not thought to be clinically significant. However, quinine and other drugs that prolong the QT interval should be used cautiously following treatment with Coartem Tablets due to the long elimination half life of lumefantrine and the potential for additive QT effects. [see *Warnings and Precautions (5.2)* and *Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Safety data from an observational pregnancy study of approximately 500 pregnant women who were exposed to Coartem Tablets (including a third of patients who were exposed in the first trimester), and published data of over 1000 pregnant patients who were exposed to artemisinin derivatives, did not show an increase in adverse pregnancy outcomes or teratogenic effects over background rate.

The efficacy of Coartem Tablets in the treatment of acute, uncomplicated malaria in pregnant women has not been established.

Coartem Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnant rats dosed during the period of organogenesis at or higher than a dose of about half the highest clinical dose of 1120 mg artemether-lumefantrine per day (based on body surface area comparisons), showed increases in fetal loss, early resorptions and post implantation loss. No adverse effects were observed in animals dosed at about one-third the highest clinical dose. Similarly, dosing in pregnant rabbits at about three times the clinical dose (based on body surface area comparisons) resulted in abortions, preimplantation loss, post implantation loss and decreases in the number of live fetuses. No adverse reproductive effects were detected in rabbits at two times the clinical dose. Embryo-fetal loss is a significant reproductive toxicity. Other artemisinins are known to be embryotoxic in animals. However, because metabolic profiles in animals and humans are dissimilar, artemether exposures in animals may not be predictive of human exposures [see *Nonclinical Toxicology (13.2)*]. These data cannot rule out an increased risk for early pregnancy loss or fetal defects in humans.

8.3 Nursing Mothers

It is not known whether artemether or lumefantrine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Coartem Tablets are administered to a nursing woman. Animal data suggest both artemether and lumefantrine are excreted into breast milk. The benefits of breastfeeding to mother and infant should be weighed against potential risk from infant exposure to artemether and lumefantrine through breast milk.

8.4 Pediatric Use

The safety and effectiveness of Coartem Tablets have been established for the treatment of acute, uncomplicated malaria in studies involving pediatric patients weighing 5 kg or more [see *Clinical Studies (14.1)*]. The safety and efficacy have not been established in pediatric patients who weigh less than 5 kg. Children from non-endemic countries were not included in clinical trials.

8.5 Geriatric Use

Clinical studies of Coartem Tablets did not include sufficient numbers of subjects aged 65 years and over to determine they respond differently from younger subjects. In general, the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in elderly patients should be considered when prescribing Coartem Tablets.

8.6 Hepatic and Renal Impairment

No specific pharmacokinetic studies have been performed in patients with either hepatic or renal impairment. Coartem Tablets have not been studied for efficacy and safety in patients with severe hepatic and/or renal impairment. No dosage adjustment is necessary in patients with mild to moderate hepatic and/or renal impairment [see *Dosage and Administration (2.4)* and *Warnings and Precautions (5.6)*].

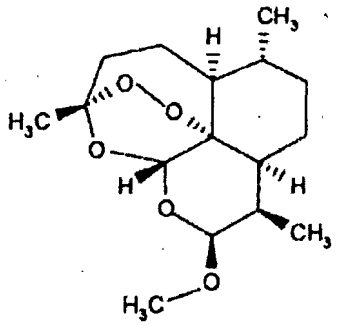
10 OVERDOSAGE

There is no information on overdoses of Coartem Tablets higher than the doses recommended for treatment.

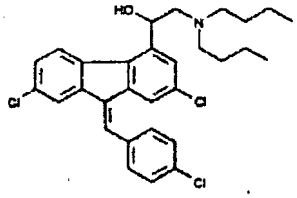
In cases of suspected overdosage, symptomatic and supportive therapy, which would include ECG and blood electrolyte monitoring, should be given as appropriate.

11 DESCRIPTION

Coartem Tablets contain a fixed combination of two antimalarial active ingredients, artemether, an artemisinin derivative, and lumefantrine. Both components are blood schizontocides. The chemical name of artemether is (3R,5aS,6R,8aS,9R,10S,12R,12aR)-decahydro-10-methoxy-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepine. Artemether is a white, crystalline powder that is freely soluble in acetone, soluble in methanol and ethanol, and practically insoluble in water. It has the empirical formula $C_{16}H_{26}O_5$ with a molecular weight of 298.4, and the following structural formula:



The chemical name of lumefantrine is (±)-2-dibutylamino-1-[2,7-dichloro-9-(4-chlorobenzylidene)-9H-fluorene-4-yl]ethanol. Lumefantrine is a yellow, crystalline powder that is freely soluble in N,N-dimethylformamide, chloroform, and ethyl acetate; soluble in dichloromethane; slightly soluble in ethanol and methanol; and insoluble in water. It has the empirical formula $C_{30}H_{32}Cl_3NO$ with a molecular weight of 528.9, and the following structural formula:



Coartem Tablets are for oral administration. Each Coartem Tablet contains 20 mg of artemether and 120 mg lumefantrine. The inactive ingredients are colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, and polysorbate 80.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Coartem Tablets, a fixed dose combination of artemether and lumefantrine in the ratio of 1:6, is an antimalarial agent [see *Clinical Pharmacology (12.4)*].

12.3 Pharmacokinetics

Absorption

Following administration of Coartem Tablets to healthy volunteers and patients with malaria, artemether is absorbed with peak plasma concentrations reached about 2 hours after dosing. Absorption of lumefantrine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma concentrations about 6 to 8 hours after administration. The single dose (4 tablets) pharmacokinetic parameters for artemether, dihydroartemisinin (DHA), an active antimalarial metabolite of artemether, and lumefantrine in adult Caucasian healthy volunteers are given in Table 3. Multiple dose data after the 6-dose regimen of Coartem Tablets in adult malaria patients are given in Table 4.

Table 3: Single Dose Pharmacokinetic Parameters[a] for Artemether, Dihydroartemisinin (DHA), and Lumefantrine under Fed Conditions

	Study 2102 (n=50)	Study 2104 (n=48)
Artemether		
C_{max} (ng/mL)	60.0 ± 32.5	83.8 ± 59.7
t_{max} (h)	1.50	2.00
AUC_{last} (ng·h/mL)	146 ± 72.2	259 ± 150
$t_{½}$ (h)	1.6 ± 0.7	2.2 ± 1.9
DHA		
C_{max} (ng/mL)	104 ± 35.3	90.4 ± 48.9
t_{max} (h)	1.76	2.00
AUC_{last} (ng·h/mL)	284 ± 83.8	285 ± 98.0
$t_{½}$ (h)	1.6 ± 0.6	2.2 ± 1.5
Lumefantrine		
C_{max} (µg/mL)	7.38 ± 3.19	9.80 ± 4.20

t_{max} (h)	6.01	8.00
AUC_{last} (µg·h/mL)	158 ± 70.1	243 ± 117
$t_{½}$ (h)	101 ± 35.6	119 ± 51.0

[a]Mean ± SD C_{max}, AUC_{last}, $t_{½}$ and Median t_{max}

Food enhances the absorption of both artemether and lumefantrine. In healthy volunteers, the relative bioavailability of artemether was increased between two- to three-fold, and that of lumefantrine sixteen-fold when Coartem Tablets were taken after a high-fat meal compared under fasted conditions. . Patients should be encouraged to take Coartem Tablets with a meal as soon as food can be tolerated [see *Dosage and Administration (2.1)*].

Distribution

Artemether and lumefantrine are both highly bound to human serum proteins *in vitro* (95.4% and 99.7%, respectively). Dihydroartemisinin is also bound to human serum proteins (47% to 76%). Protein binding to human plasma proteins is linear.

Biotransformation

In human liver microsomes and recombinant CYP450 enzymes, the metabolism of artemether was catalyzed predominantly by CYP3A4/5. Dihydroartemisinin (DHA) is an active metabolite of artemether. The metabolism of artemether was also catalyzed to a lesser extent by CYP2B6, CYP2C9 and CYP2C19. *In vitro* studies with artemether at therapeutic concentrations revealed no significant inhibition of the metabolic activities of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and CYP4A9/11.

During repeated administration of Coartem Tablets, systemic exposure of artemether decreased significantly, while concentrations of DHA increased, although not to a statistically significant degree. The artemether/DHA AUC ratio is 1.2 after a single dose and 0.3 after 6 doses given over 3 days. This suggests that there was induction of CYP3A4/5 responsible for the metabolism of artemether.

In human liver microsomes and in recombinant CYP450 enzymes, lumefantrine was metabolized mainly by CYP3A4 to desbutyl-lumefantrine. The systemic exposure to the metabolite desbutyl-lumefantrine was less than 1% of the exposure to the parent compound. *In vitro,* lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations.

Caution is recommended when combining Coartem Tablets with substrates, inhibitors, or inducers of CYP3A4, especially anti-retroviral drugs and those that prolong the QT interval (e.g., macrolide antibiotics, pimozide, terfenadine, astemizole, cisapride) [see *Warnings and Precautions (5.1, 5.3)*].

Co-administration of Coartem Tablets with CYP2D6 substrates may result in increased plasma concentrations of the CYP2D6 substrate and increase the risk of adverse reactions. In addition, many of the drugs metabolized by CYP2D6 can prolong the QT interval and should not be administered with Coartem Tablets due to the potential additive effect on the QT interval (e.g., flecainide, imipramine, amitriptyline, clomipramine) [see *Warnings and Precautions (5.1, 5.4)*].

Elimination

Artemether and DHA are cleared from plasma with an elimination half-life of about 2 hours. Lumefantrine is eliminated more slowly, with a terminal half-life of 3-6 days in healthy volunteers and in patients with *falciparum* malaria. Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics of artemether and lumefantrine.

No urinary excretion data are available for humans. In animal studies, artemether metabolites were largely excreted in the urine. However, urinary excretion of artemether, lumefantrine and lumefantrine metabolites was negligible. While animal data are informative, they do not always predict human results.

Hepatic and Renal Impairment

No specific pharmacokinetic studies have been performed in patients with either hepatic or renal impairment [see *Dosage and Administration (2.4)*].

Pediatric Patients

The PK of artemether, DHA, and lumefantrine were obtained in two pediatric studies by sparse sampling using a population based approach. PK estimates derived from a composite plasma concentration profile for artemether, DHA, and lumefantrine are provided in Table 4.

Systemic exposure to artemether, DHA, and lumefantrine, when dosed on a mg/kg body weight basis in pediatric patients ($\geq$5 to <35 kg body weight), is comparable to that of the recommended dosing regimen in adult patients.

Table 4: Summary of Pharmacokinetic Parameters for Lumefantrine, Artemether and DHA in Pediatric and Adult Patients with Malaria Following Administration of a 6-dose Regimen of Coartem Tablets

		Pediatric patients (body weight, kg)[1]		
Drug	Adults[2]	5 - < 15	15 - < 25	25 - < 35
Lumefantrine				
Mean Cmax, range (μg/mL)	5.60 - 9.0	4.71 – 12.6		Not Available
Mean AUClast, range (μg·h/mL)	410 - 561	372 – 699		Not Available
Artemether				
Mean Cmax ± SD (ng/mL)	186 ± 125	223 ± 309	198 ± 179	174 ± 145
Dihydroartemisinin				
Mean Cmax ± SD (ng/mL)	101 ± 58	54.7 ± 58.9	79.8 ± 80.5	65.3 ± 23.6

[1] There are 477 children for the lumefantrine pharmacokinetic parameters; for artemether and dihydroartemisinin pharmacokinetic parameters there are 55, 29, and 8 children for the 5 to < 15, 15 to < 25 and the 25 to < 35 kg groups, respectively.

[2] There are a total of 181 adults for lumefantrine pharmacokinetic parameters and a total of 25 adults for artemether and dihydroarthemisin pharmacokinetic parameters.

Geriatric Patients

No specific pharmacokinetic studies have been performed in patients older than 65 years of age.

Drug Interactions

Ketoconazole (potent CYP3A4 inhibitor)

Concurrent oral administration of ketoconazole (400 mg on Day 1 followed by 200 mg on days 2, 3, 4 and 5) with Coartem Tablets (single dose of 4 tablets of 20 mg artemether/120 mg lumefantrine per tablet) with a meal led to an increase in exposure, in terms of area under the curve (AUC), of artemether (2.3-fold), DHA (1.5 fold), and lumefantrine (1.6-fold) in 13 healthy subjects. The pharmacokinetics of ketoconazole were not evaluated. Based on this study, dose adjustment of Coartem Tablets is considered unnecessary when administered with ketoconazole or other CYP3A4 inhibitors. However, due to the potential for increased concentrations of lumefantrine which could lead to QT prolongation, Coartem Tablets should be used cautiously with other drugs that inhibit CYP3A4 (e.g., anti-retroviral drugs, macrolide antibiotics, antidepressants, imidazole antifungal agents) [see *Warnings and Precautions (5.1, 5.3)*].

Antimalarials

The oral administration of mefloquine in 14 healthy volunteers administered as three doses of 500 mg, 250 mg and 250 mg, followed 12 hours later by Coartem Tablets (6 doses of 4 tablets of 20 mg artemether/120 mg lumefantrine per tablet), had no effect on plasma concentrations of artemether or the artemether/DHA ratio. In the same study, there was a 30% reduction in C_{max} and 40% reduction in AUC of lumefantrine, possibly due to lower absorption secondary to a mefloquine-induced decrease in bile production.

Intravenous administration of a single dose of quinine (10 mg/kg bodyweight) concurrent with the last dose of a 6-dose regimen of Coartem Tablets had no effect on systemic exposure of DHA, lumefantrine or quinine in 14 healthy volunteers. Mean AUC of artemether were 46% lower when administered with quinine compared to Coartem Tablets alone. This decrease in artemether exposure is not thought to be clinically significant. However, quinine should be used cautiously in patients following treatment with Coartem Tablets due to the long elimination half-life of lumefantrine and the potential for additive effects on the QT interval [see *Warnings and Precautions (5.2)*].

Anti-Retroviral Drugs

No formal drug-drug interaction studies between Coartem Tablets and Anti-Retroviral drugs (ARTs), such as protease inhibitors, non-nucleoside reverse transcriptase inhibitors, have been performed. Due to variable patterns of inhibition, induction or competition for CYP3A4 with anti-retroviral drugs, Coartem Tablets should be used cautiously in patients on ARTs as the result may be an increase in lumefantrine concentrations causing QT prolongation, a decrease in concentrations of the ART resulting in loss of efficacy, or a decrease in artemether and/or lumefantrine concentrations resulting in loss of antimalarial efficacy of Coartem Tablets [see *Warnings and Precautions (5.3)*].

Hormonal Contraceptives

No formal drug-drug interaction studies between Coartem Tablets and hormonal contraceptives have been performed. However, artemether may induce CYP3A4/5, reducing the effectiveness of hormonal contraceptives [see *Warnings and Precautions (5.3)*].

12.4 Microbiology

Mechanism of Action

Coartem Tablets, a fixed ratio of 1:6 parts of artemether and lumefantrine, respectively, is an antimalarial agent. Artemether is rapidly metabolized into an active metabolite dihydroartemisinin (DHA). The anti-malarial activity of artemether and DHA has been attributed to endoperoxide moiety. The exact mechanism by which lumefantrine, exerts its anti-malarial effect is not well defined. Available data suggest lumefantrine inhibits the formation of β-hematin by forming a complex with hemin. Both artemether and lumefantrine were shown to inhibit nucleic acid and protein synthesis.

Activity In Vitro and In Vivo

Artemether and lumefantrine are active against the erythrocytic stages of *Plasmodium falciparum*.

Drug Resistance

Strains of *P. falciparum* with a moderate decrease in susceptibility to artemether or lumefantrine alone can be selected *in vitro* or *in vivo*, but not maintained in the case of artemether. The clinical relevance of such an effect is not known.

12.5 Effects on the Electrocardiogram

In a healthy adult volunteer parallel group study including a placebo and moxifloxacin control group (n=42 per group), the administration of the 6-dose regimen of Coartem Tablets was associated with prolongation of QTcF (Fridericia). Following administration of a 6-dose regimen of Coartem Tablets consisting of 4 tablets per dose (total of 4 tablets of 80 mg artemether/480 mg lumefantrine) taken with food, the maximum mean change from baseline and placebo adjusted QTcF was 7.5 msec (1-sided 95% Upper CI: 11 msec). There was a concentration-dependent increase in QTcF for lumefantrine.

In clinical trials conducted in children, no patient had QTcF >500 msec. Over 5% of patients had an increase in QTcF of over 60 msec.

In clinical trials conducted in adults, QTcF prolongation of >500 msec was reported in 3 (0.3%) of patients. Over 6% of adults had a QTcF increase of over 60 msec from baseline.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were not conducted.

Mutagenesis

No evidence of mutagenicity was detected. The artemether: lumefantrine combination was evaluated using the *Salmonella* and *Escherichia*/mammalian-microsome mutagenicity test, the gene mutation test with Chinese hamster cells V79, the cytogenetic test on Chinese hamster cells *in vitro*, and the rat micronucleus test, *in vivo*.

Impairment of Fertility

Pregnancy rates were reduced by about one half in female rats dosed for 2 to 4 weeks with the artemether-lumefantrine combination at 1000 mg/kg (about 9 times the clinical dose based on body surface area comparisons). Male rats dosed for 70 days showed increases in abnormal sperm (87 % abnormal) and increased testes weights at 30 mg/kg doses (about one third the clinical dose). Higher doses (about 9 times the clinical dose) resulted in decreased sperm motility and 100 % abnormal sperm cells.

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicity

Pregnant rats dosed during the period of organogenesis, at or higher than 60 mg/kg/day with the artemether-lumefantrine combination (a dose about half the highest clinical dose based on body surface area comparisons), showed increases in the number of dead fetuses, early resorptions and post implantation losses. No adverse effects were observed in animals dosed at 40 mg/kg (about one third the clinical dose). Similarly, dosing in pregnant rabbits at 175 mg/kg/day (about three times the highest clinical dose based on body surface area comparisons) resulted in abortions, preimplantation losses, post

implantation losses, and decreases in the number of live fetuses. No adverse reproductive effects were detected in rabbits at 105 mg/kg/day, about two times the clinical dose based on body surface area comparisons.

Other artemisinins are known to be embryotoxic in animals. Reproductive toxicity studies with artemisinin derivatives (e.g, artesunate) demonstrated increased post-implantation loss and teratogenicity (a low incidence of cardiovascular and skeletal malformations) in rats and rabbits. Similar findings were not seen in animal reproductive studies using artemether.

Neurotoxicity

Studies in dogs and rats have shown that intramuscular injections of artemether resulted in brain lesions. Changes observed mainly in brainstem nuclei included chromatolysis, eosinophilic cytoplasmic granulation, spheroids, apoptosis, and dark neurons. Lesions were observed in rats dosed with artemether at 25 mg/kg for 7 or 14 days and dogs dosed at 20 mg/kg for 8 days or longer, but lesions were not observed after shorter courses of drug or after oral dosing. The estimated artemether 24 h AUC after 7 days of dosing at the no observed effect level (10 mg/kg/day given intramuscularly) is approximately 7-fold greater than the estimated artemether 24 h AUC in humans on day 1 of the standard 3-day oral treatment regimen; oral exposure in humans decreases on subsequent days, thus the exposure margin increases. Dogs dosed orally with 143 mg/kg artemether showed a statistically measureable effect on the hearing threshold at 20 dB. This dose is equivalent to about 29 times the highest artemether clinical dose (160 mg/day) based on body surface area comparisons. Most nervous system disorder adverse events in the studies of the 6-dose regimen were mild in intensity and resolved by the end of the study [see *Adverse Reactions (6.2)*].

14 CLINICAL STUDIES

14.1 Treatment of Acute, Uncomplicated *P. falciparum* Malaria

The efficacy of Coartem Tablets was evaluated for the treatment of acute, uncomplicated malaria caused by *P. falciparum* in HIV negative patients in 8 clinical studies. Uncomplicated malaria was defined as symptomatic *P. falciparum* malaria without signs and symptoms of severe malaria or evidence of vital organ dysfunction. Baseline parasite density ranged from 500/μL - 200,000/μL (0.01% to 4% parasitemia) in the majority of patients. Studies were conducted in partially immune and non-immune adults and children (≥5kg body weight) with uncomplicated malaria in China, Thailand, sub-Saharan Africa, Europe, and South America. Patients who had clinical features of severe malaria, severe cardiac, renal, or hepatic impairment were excluded.

The studies include two 4-dose studies assessing the efficacy of the components of the regimen, a study comparing a 4-dose versus a 6-dose regimen, and 5 additional 6-dose regimen studies.

Coartem Tablets were administered at 0, 8, 24, and 48 hours in the 4-dose regimen, and at 0, 8, 24, 36, 48, and 60 hours in the 6-dose regimen. Efficacy endpoints consisted of:

- 28 day cure rate, defined as clearance of asexual parasites (the erythrocytic stage) within 7 days without recrudescence by day 28
- parasite clearance time (PCT), defined as time from first dose until first total and continued disappearance of asexual parasite which continues for a further 48 hours
- fever clearance time (FCT), defined as time from first dose until the first time body temperature fell below 37.5°C and remained below 37.5°C for at least a further 48 hours (only for patients with temperature > 37.5°C at baseline)

The modified intent to treat (mITT) population includes all patients with malaria diagnosis confirmation who received at least one dose of study drug. Evaluable patients generally are all patients who had a day 7 and a day 28 parasitological assessment or experienced treatment failure by day 28.

Studies 1 and 2: The two studies which assessed the efficacy of Coartem Tablets (4 doses of 4 tablets of 20 mg artemether/120 mg lumefantrine) compared to each component alone were randomized, double-blind, comparative, single center, conducted in China. The efficacy results (Table 5) support that the combination of artemether and lumefantrine in Coartem Tablets had a significantly higher 28-day cure rate compared to artemether and had a significantly faster parasite clearance time (PCT) and fever clearance time (FCT) compared to lumefantrine.

Table 5: Clinical Efficacy of Coartem Tablets versus Components (mITT Population[1]

Study No. **Region/patient ages**	**28-day cure rate[2]** n/N (%) patients	**Median FCT[3]** [25th,75th percentile]	**Median PCT** [25th,75th percentile]
Study 1 China, ages 13 - 57 years			
Coartem Tablets	50/51 (98.0)	24 hours [9, 48]	30 hours [24, 36]
Artemether[4]	24/52 (46.2)	21 hours [12, 30]	30 hours [24, 33]
Lumefantrine[5]	47/52 (90.4)	60 hours [36, 78]	54 hours [45, 66]
Study 2 China, ages 12 - 65 years			
Coartem Tablets	50/52 (96.2)	21 hours [6, 33]	30 hours [24, 36]
Lumefantrine[6]	45/51 (88.2)	36 hours [12, 60]	48 hours [42, 60]

[1]In mITT analysis, patients whose status was uncertain were classified as treatment failures.
[2]Efficacy cure rate based on blood smear microscopy.
[3]For patients who had a body temperature > 37.5°C at baseline only
[4]95% CI (Coartem Tablets – artemether) on 28-day cure rate: 37.8%, 66.0%
[5]P-value comparing Coartem Tablets to lumefantrine on parasite clearance time (PCT) and fever clearance time (FCT): < 0.001
[6]P-value comparing Coartem Tablets to lumefantrine on parasite clearance time (PCT): < 0.001 and on fever clearance time (FCT): < 0.05

Results of 4-dose studies conducted in areas with high resistance such as Thailand during 1995-96 showed lower efficacy results than the above studies. Therefore, Study 3 was conducted.

Study 3: Study 3 was a randomized, double-blind, two-center study conducted in Thailand in adults and children (aged ≥2 years), which compared the 4-dose regimen (administered over 48 hours) of Coartem Tablets to a 6-dose regimen (administered over 60 hours). Twenty-eight day cure rate in mITT subjects was 81% (96/118) for the Coartem Tablets 6-dose arm as compared to 71% (85/120) in the 4-dose arm.

Studies 4, 5, 6, 7, and 8: In these studies, Coartem Tablets were administered as the 6-dose regimen.

In study 4, a total of 150 adults and children aged ≥2 years received Coartem Tablets. In study 5, a total 164 adults and children ≥12 years received Coartem Tablets. Both studies were conducted in Thailand.

Study 6 was a study of 165 non-immune adults residing in regions non-endemic for malaria (Europe and Colombia) who contracted acute uncomplicated *falciparum* malaria when traveling in endemic regions.

Study 7 was conducted in Africa in 310 infants and children aged 2 months to 9 years, weighing 5 kg to 25 kg, with an axillary temperature ≥37.5 °C.

Study 8 was conducted in Africa in 452 infants and children, aged 3 months to 12 years, weighing 5 kg to < 35 kg, with fever (≥37.5°C axillary or ≥38°C rectally) or history of fever in the preceding 24 hours.

Results of 28-day cure rate, median parasite clearance time (PCT), and fever clearance time (FCT) for Studies 3 to 8 are reported in Table 6.

Table 6: Clinical Efficacy of 6-dose Regimen of Coartem Tablets

Study No. Region/ages	28-day cure rate[1] n/N (%) patients		Median FCT[2]	Median PCT
	mITT[3]	Evaluable	[25th, 75th percentile]	[25th, 75th percentile]
Study 3 Thailand, ages 3 – 62 years	96/118 (81.4)	93/96 (96.9)	35 hours	44 hours
Early failure[4]	0	0	[20, 46]	[22, 47]
Late failure[5]	4 (3.4)	3 (3.1)		
Lost to follow up	18 (15.3)			
Other[6]	0			
Study 4 Thailand, ages 2 – 63 years	130/149 (87.2)	130/134 (97.0)	22 hours	NA
Early failure[4]	0	0	[19, 44]	
Late failure[5]	4 (2.7)	4 (3.0)		
Lost to follow up	13 (8.7)			
Other[6]	2 (1.3)			
Study 5 Thailand, ages 12 – 71 years	148/164 (90.2)	148/155 (95.5)	29 hours	29 hours
Early failure[4]	0	0	[8, 51]	[18, 40]
Late failure[5]	7 (4.3)	7 (4.5)		
Lost to follow up	9 (5.5)			
Other[6]	0			
Study 6				

Europe/Columbia, ages 16 – 66 years	120/162 (74.1)	119/124 (96.0)	37 hours [18, 44]	42 hours [34, 63]
Early failure[4]	6 (3.7)	1 (0.8)		
Late failure[5]	3 (1.9)	3 (2.4)		
Lost to follow up	17 (10.5)			
Other[6]	16 (9.9)	1 (0.8)		
Study 7 Africa, ages 2 months – 9 years	268/310 (86.5)	267/300 (89.0)	8 hours [8, 24]	24 hours [24, 36]
Early failure[4]	2 (0.6)	0		
Late failure[5]	34 (11.0)	33 (11.0)		
Lost to follow up	2 (0.6)			
Other[6]	4 (1.3)			
Study 8 Africa, ages 3 months – 12 years	374/452 (82.7)	370/419 (88.3)	8 hours [8, 23]	35 hours [24, 36]
Early failure[4]	13 (2.9)	0		
Late failure[5]	49 (10.8)	49 (11.7)		
Lost to follow up	6 (1.3)			
Other[6]	10 (2.2)			

[1] Efficacy cure rate based on blood smear microscopy
[2] For patients who had a body temperature > 37.5°C at baseline only
[3] In mITT analysis, patients whose status was uncertain were classified as treatment failures.
[4] Early failures were usually defined as patients withdrawn for unsatisfactory therapeutic effect within the first 7 days or because they received another antimalarial medication within the first 7 days
[5] Late failures were defined as patients achieving parasite clearance within 7 days but having parasite reappearance including recrudescence or new infection during the 28 day follow-up period
[6] Other includes withdrawn due to protocol violation or non-compliance, received additional medication after day 7, withdrew consent, missing day 7 or 28 assessment

In all studies, patients' signs and symptoms of malaria resolved when parasites were cleared.

In studies conducted in areas with high transmission rates, such as Africa, reappearance of *P. falciparum* parasites may be due to recrudescence or a new infection.

The efficacy by body weight category for studies 7 and 8 is summarized in Table 7.

Table 7: Clinical Efficacy by Weight for Pediatric Studies

Study No. Age category	Coartem Tablets 6-dose Regimen		
	mITT population[1]		Evaluable population
	Median PCT [25th,75th percentile]	28-day cure rate[2] n/N (%) patients	28-day cure rate[2] n/N (%) patients
Study 7			
5 - <10 kg	24 [24, 36]	133/154 (86.4)	133/149 (89.3)
10 - <15 kg	35 [24, 36]	94/110 (85.5)	94/107 (87.9)
15 -25 kg	24 [24, 36]	41/46 (89.1)	40/44 (90.9)
Study 8[3]			
5 - <10 kg	36 [24, 36]	61/83 (73.5)	61/69 (88.4)
10 - <15 kg	35 [24, 36]	160/190 (84.2)	157/179 (87.7)
15 - <25 kg	35 [24, 36]	123/145 (84.8)	123/140 (87.9)

25 - <35 kg	26 [24, 36]	30/34 (88.2)	29/31 (93.5)

[1] In mITT analysis, patients whose status was uncertain were classified as treatment failures.
[2] Efficacy cure rate based on blood smear microscopy
[3] Coartem Tablets administered as crushed tablets

The efficacy of Coartem Tablets for the treatment *P. falciparum* infections mixed with *P. vivax* was assessed in a small number of patients. Coartem Tablets are only active against the erythrocytic phase of *P. vivax* malaria. Of the 43 patients with mixed infections at baseline, all cleared their parasitemia within 48 hours. However, parasite relapse occurred commonly (14 /43; 33%). Relapsing malaria caused by *P. vivax* requires additional treatment with other antimalarial agents to achieve radical cure i.e., eradicate any hypnozoite forms that may remain dormant in the liver.

16 HOW SUPPLIED/STORAGE AND HANDLING

Coartem (artemether/lumefantrine) Tablets

20mg/120mg Tablets - yellow, round flat tablets with beveled edges and scored on one side. Tablets are imprinted with N/C on one side and CG on the other.

Bottle of 24	NDC 0078-0568-45
Unit dose carton of 24 tablets (4 x 6-tablet blister cards)	NDC 0078-0568-43

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see *USP Controlled Room Temperature*].

Dispense in tight container (USP).

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.2).

17.1 Information for Safe Use

- Instruct patients to take Coartem Tablets with food. Patients who do not have an adequate intake of food are at risk for recrudescence of malaria.
- Patients hypersensitive to artemether, lumefantrine, or to any of the excipients should not receive Coartem Tablets.
- Instruct patients to inform their physician of any personal or family history of QT prolongation or proarrhythmic conditions such as hypokalemia, bradycardia, or recent myocardial ischemia.
- Instruct patients to inform their physician if they are taking any other medications that prolong the QT interval, such as class IA (quinidine, procainamide, disopyramide), or class III (amiodarone, sotalol) antiarrhythmic agents; antipsychotics (pimozide, ziprasidone); antidepressants; certain antibiotics (macrolide antibiotics, fluoroquinolone antibiotics, imidazole, and triazole antifungal agents); certain non-sedating antihistamines (terfenadine, astemizole), or cisapride.
- Instruct patients to notify their physicians if they have any symptoms of prolongation of the QT interval, including prolonged heart palpitations or a loss of consciousness.

- Instruct patients to avoid medications that are metabolized by the cytochrome enzyme CYP2D6 while receiving Coartem Tablets since these drugs also have cardiac effects (e.g., flecainide, imipramine, amitriptyline, clomipramine).
- Inform patients that based on animal data, Coartem Tablets administered during pregnancy may result in fetal loss. Fetal defects have been reported when artemisinins are administered to animals.
- Halofantrine and Coartem Tablets should not be administered within one month of each other due to potential additive effects on the QT interval.
- Antimalarials should not be given concomitantly with Coartem Tablets, unless there is no other treatment option, due to limited safety data.
- QT prolonging drugs, including quinine and quinidine, should be used cautiously following Coartem Tablets due to the long elimination half-life of lumefantrine and the potential for additive effects on the QT interval.
- Closely monitor food intake in patients who received mefloquine immediately prior to treatment with Coartem Tablets.
- Use Coartem Tablets cautiously in patients receiving other drugs that are substrates, inhibitors or inducers of CYP3A4, including grapefruit juice, especially those that prolong the QT interval or are anti-retroviral drugs.
- Coartem Tablets may reduce the effectiveness of hormonal contraceptives. Therefore, patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control.
- Inform patients that Coartem Tablets can cause hypersensitivity reactions. Instruct patients to discontinue the drug at the first sign of a skin rash, hives or other skin reactions, a rapid heartbeat, difficulty in swallowing or breathing, any swelling suggesting angioedema (e.g., swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction.

17.2 FDA-Approved Patient Labeling

Patient Information

Coartem®

(co-AR-tem)

(artemether and lumefantrine)

Tablets

Read this patient information before you start taking Coartem. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is Coartem?

Coartem is a prescription medicine used to treat uncomplicated malaria in adults and children who weigh at least 11 pounds (5 kg).

Who should not take Coartem?

Do not take Coartem if you are allergic to any of the ingredients. See the end of this leaflet for a complete list of ingredients in Coartem.

What should I tell my healthcare provider before taking Coartem?

Before you take Coartem, tell your healthcare provider about all your medical conditions including if you have:

- heart disease or a family history of heart problems or heart disease
- liver or kidney problems
- recently taken other medicines used to treat malaria
- if you are pregnant or are planning to become pregnant. Coartem may increase your risk for loss of pregnancy. Fetal defects have been reported when artemisinins are administered to animals. Talk to your healthcare provider before taking Coartem.
- if you are breast-feeding. It is not known if Coartem passes into your breast milk. You and your doctor will decide the best way to feed your baby if you take Coartem.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Coartem and other medicines may affect each other causing side effects. Coartem may affect the way other medicines work and other medicines may affect how Coartem works.

Especially tell your doctor if you take:

- any other medicines to treat or prevent malaria
- medicines for your heart

- antipsychotic medicines
- antidepressants
- antibiotics
- antihistamines
- Cisapride (Propulsid®)
- medicines to treat HIV-infection
- hormonal methods of birth control (for example, birth control pills or patch)

Ask your healthcare provider if you are not sure if your medicine is one that is listed above. Know the medicines you take. Keep a list of your medicines with you to show your healthcare providers when you get a new medicine.

How should I take Coartem?

- Take Coartem exactly as prescribed.
- If you weigh 77 pounds (35 kg) or more, one dose of Coartem is 4 tablets.
- If you weigh less than 77 pounds (35 kg), your healthcare provider will tell you how many tablets to take for each dose.
- A full course of treatment is 6 doses of Coartem taken over 3 days:

  Day 1: take 1 dose; 8 hours later take 1 dose

  Day 2: take 1 dose in the morning, 1 dose in the evening

  Day 3: take 1 dose in the morning, 1 dose in the evening

  Take Coartem for 3 days even if you are feeling better.
- Every dose of Coartem should be taken with food, such as milk, infant formula pudding, porridge, or broth. It is important for you to eat as soon as you can so that your malaria will go away and not get worse.
- Do not drink grapefruit juice while you take Coartem. Drinking grapefruit juice during treatment with Coartem can cause you to have too much medicine in your blood.
- Coartem may be crushed and mixed with one to two teaspoons of water in a clean container.
- If you vomit within 1 hour of taking Coartem you should take another dose of Coartem. If you vomit the second dose, tell your healthcare provider. A different medicine may need to be prescribed for you.

Tell your healthcare provider right away if:

- your malaria does not get better
- you vomited any of your doses of Coartem
- you are not able to eat

- you get flu-like symptoms (chills, fever, muscle pains, or headaches) again after you have finished your treatment with Coartem.
- you have any change in the way your heart beats or a loss of consciousness (fainting).

What are the possible side effects of Coartem?

Coartem can cause serious side effects including:

- **A heart problem called QT prolongation** that can cause an abnormal heartbeat can happen in people who take Coartem. The chance of this happening is higher in people with a family history of prolonged QT interval, low potassium (hypokalemia), and in people who take medicines to control heartbeats.
- **Allergic reactions.** Symptoms of an allergic reaction include: rash, hives, fast heartbeat, trouble swallowing or breathing, swelling of lips, tongue, face, tightness of the throat, or trouble speaking. If you have a serious allergic reaction, stop taking Coartem and get emergency medical help right away.

The most common side effects in adults are:

- headache
- feeling dizzy
- feeling weak
- loss of appetite
- muscle and joint pain or stiffness
- feeling tired
- chills
- fever

The most common side effects in children are:

- fever
- cough
- vomiting
- headache
- loss of appetite

These are not all the possible side effects of Coartem. For more information, ask your doctor or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Coartem?

Store Coartem between 59°F to 86°F (15°C to 30°C).

Keep Coartem and all medicines out of the reach of children.

General information about the safe and effective use of Coartem.

Medicines are sometimes prescribed for purposes other than those listed in patient information leaflets. Do not use Coartem for a condition for which it was not prescribed. Do not give Coartem to other people, even if they have the same symptoms that you have. It may harm them.

This patient information leaflet summarizes the most important information about Coartem. If you would like more information about Coartem talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about Coartem that is written for health professionals. For more information call 1-888-294-6287.

What are the ingredients in Coartem?

Active ingredients include: artemether, lumefantrine

Inactive ingredients include: colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polysorbate 80

Distributed by:

Novartis Pharmaceuticals Corporation

East Hanover, New Jersey 07936

April 2009 T2008-64/T2008-65

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-268

NDA APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Susan Kummerer, M.S.
Director, Drug Regulatory Affairs
One Health Plaza, Bldg. 405/4051
East Hanover, NJ 07936-1080

Dear Ms. Kummerer:

Please refer to your new drug application (NDA) dated June 27, 2008, received June 27, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Coartem (artemether 20 mg/lumefantrine 120 mg) Tablets.

We note that NDA 22-268 was submitted for the indication of treatment of malaria in patients of 5 kg bodyweight or above with acute, uncomplicated malaria due to *Plasmodium falciparum* or mixed infections including *P. falciparum*. Please note, as was described to you by Ms. Diana Willard, Chief, Project Management Staff, via telephone on April 7, 2009 NDA 22-268 will be for the indication of the treatment of acute, uncomplicated malaria infections due to *P. falciparum*. b(4)

We acknowledge receipt of your submissions dated:

September 5, 2008 (2)	October 6, 2008	November 11, 2008	December 18, 2008 (3)
September 9, 2008 (2)	October 8, 2008	November 17, 2008 (2)	December 22, 2008 (2)
September 10, 2008	October 13, 2008	November 21, 2008 (2)	February 12, 2009
September 11, 2008	October 16, 2008	November 25, 2008 (3)	February 13, 2009
September 12, 2008	October 28, 2008	December 1, 2008	February 19, 2009
September 15, 2008 (2)	October 30, 2008 (2)	December 4, 2008	March 6, 2009
September 16, 2008 (2)	October 31, 2008 (2)	December 9, 2008	March 11, 2009
September 19, 2008	November 5, 2008	December 12, 2008	March 18, 2009
October 1, 2008 (3)	November 6, 2008 (3)	December 15, 2008	March 26, 2009

This new drug application provides for the use of Coartem (artemether/lumefantrine) Tablets for the treatment of acute, uncomplicated malaria infections due to *Plasmodium falciparum* in patients of 5 kg bodyweight and above.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 22-268."

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton, immediate container labels, and wallet blister labels that are identical to the carton, immediate container labels, and wallet blister labels submitted December 18, 2008 as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-268.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text and in the required format may render the product misbranded and an unapproved new drug.

TROPICAL DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a tropical disease priority review voucher, as provided under section 524 of the FDCA. This voucher entitles you to designate a single human drug application submitted under section 505(b)(1) of the FD&C Act or section 351 of the PHS Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. This priority review voucher may be transferred by you to another sponsor of a human drug application. When redeeming this priority review voucher you should refer to this letter as an official record of the voucher. If the voucher is transferred, the sponsor to whom the voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the voucher was transferred. In addition, this priority review voucher has been assigned a tracking number, *PRV* 22268. All correspondences related to this voucher should refer to this tracking number. For additional information regarding the priority review voucher, please see FDA's guidance for industry titled "Tropical Disease Priority Review Vouchers" at http://www.fda.gov/cder/guidance/index.htm.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Since this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess signals of serious risk of neurologic or cardiac adverse reactions, and of genotoxicity related to lumefantrine or artemether impurities; or to identify an unexpected serious risk arising from treatment failure due to drug resistance, altered metabolism of co-administered drugs, or drug-drug interactions.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to:

1. **Conduct a descriptive study of the use of Coartem Tablets in non-immune travelers.**

   For a period of five years following approval, collect baseline patient demographic information (including age, weight, height, sex, race, prior medications and concomitant medications, as well as immune status), adverse reactions, including potential nervous system and cardiac adverse reactions, and efficacy outcomes. You should include representation of adults > 65 years, children ≤16 years, and overweight patients (BMI ≥25 kg/m^2). Submit yearly reports summarizing data on patients treated with Coartem Tablets within the previous year and the final report integrating information on all patients in the Final Report Submission.

   The timetable you submitted on March 26, 2009 states that you will conduct this study according to the following timetable:

Final Protocol Submission:	by March 2010
Study Start Date:	by October 2010
Final Report Submission:	by April 2016

2. **Submit surveillance reports to evaluate the potential development of resistance to Coartem Tablets.**

   For a period of five years following approval, submit a yearly report describing the reported resistance to a combination of artemether and lumefantrine in malaria endemic countries as obtained from ongoing resistance monitoring programs on antimalarials collected by international consortia and organizations (e.g., World Health Organization).

The timetable you submitted on March 26, 2009 states that you will fulfill this requirement according to the following timetable:

Submission of Study Report Plan:	by July 2009
Study Reporting Start Date:	by October 2009
Final Report Submission:	by August 2016

3. **Conduct a neurotoxicity study of oral artemether in juvenile rats including neurologic functional batteries, toxicokinetics, and extensive brain histopathology.**

Conduct a neurotoxicity study of oral artemether in juvenile rats to assess how exposure and toxicity in young animals compares with older animals and humans, and whether neurologic deterioration occurs following the terminal dose. This study should consist of a main study group, a toxicokinetic group, and a recovery group. In this study, comprehensive histopathological examination of the central nervous system should be conducted.

The timetable you submitted on March 26, 2009 states that you will conduct this study according to the following timetable:

Final Protocol Submission:	by July 2009
Study Start Date:	by December 2009
Final Report Submission:	by December 2011

4. **Conduct bacterial reverse mutation studies (Ames assays) for lumefantrine impurities [redacted] and artemether impurities [redacted]**

Lumefantrine impurities [redacted] and artemether impurities [redacted] have structural alerts for genotoxicity, and the proposed release limits for these compounds are higher than levels that are qualified by available toxicology studies.

The timetable you submitted on March 26, 2009 states that you will conduct this study according to the following timetable:

Study Start Date:	by December 2009
Final Report Submission:	by June 2010

5. **Perform spectral characterization of all specified impurities for lumefantrine impurities [redacted] and artemether impurities [redacted]**

The structure of lumefantrine impurities [redacted] and artemether impurities [redacted] should be characterized using spectral procedures such as ^{1}H- and ^{13}C-NMR (nuclear magnetic resonance), infrared (IR), ultraviolet and mass spectroscopy. Tabulated, interpreted data for all spectra, and copies of IR and ^{1}H-NMR spectra should be submitted.

The timetable you submitted on March 26, 2009 states that you will conduct this study according to the following timetable:

Study Start Date:	by June 2009
Final Report Submission:	by December 2009

6. **Conduct an *in vitro* study to characterize the induction potential of artemether, dihydroartemisinin (DHA), and lumefantrine on the metabolism of substrates of CYP3A4.**

Conduct an *in vitro* study to evaluate the induction potential of artemether, DHA, and lumefantrine on the metabolism of co-administered drugs that are substrates of the Cytochrome P450 3A4 (CYP3A4) enzyme system (e.g., oral contraceptives). Refer to the guidance for industry titled *Drug Interaction Studies--Study Design, Data Analysis, and Implications for Dosing and Labeling* (http://www.fda.gov/cder/guidance/6695dft.pdf) for details on the conduct of the *in vitro* study.

If the results of this *in vitro* study are positive, a clinical trial will be needed to further assess this risk (see Item 14, below).

The timetable you submitted on March 26, 2009 states that you will conduct this study according to the following timetable:

Final Protocol Submission:	by December 2009
Study Start Date:	by March 2010
Final Report Submission:	by March 2011

7. **Conduct an *in vitro* study to characterize the potential interaction between artemether and lumefantrine, the components of Coartem Tablets, and rifampin.**

If, upon review, it is determined that the clinical trial discussed in Item 11 below adequately addresses the potential interaction between artemether and lumefantrine and rifampin, then this *in vitro* study will not be needed. Otherwise, refer to the guidance for industry titled *Drug Interaction Studies--Study Design, Data Analysis, and Implications for Dosing and Labeling* for details on the conduct of the *in vitro* study.

The timetable you submitted on March 26, 2009 states that you will conduct this study according to the following timetable:

Final Protocol Submission:	by June 2011
Study Start Date:	by January 2012
Final Report Submission:	by January 2013

8. **Conduct an *in vitro* study to characterize the potential interaction between artemether and lumefantrine, the components of Coartem Tablets, and protease inhibitors (PIs).**

If, upon review, it is determined that the clinical trial discussed in Item 12 below adequately addresses the potential interaction between artemether and lumefantrine and

PIs, then this *in vitro* study will not be needed. Otherwise, refer to the guidance for industry titled *Drug Interaction Studies--Study Design, Data Analysis, and Implications for Dosing and Labeling* for details on the conduct of the *in vitro* study.

The timetable you submitted on March 26, 2009 states that you will conduct this study according to the following timetable:

Final Protocol Submission:	by June 2011
Study Start Date:	by January 2012
Final Report Submission:	by January 2013

9. **Conduct an *in vitro* study to characterize the potential interaction between artemether and lumefantrine, the components of Coartem Tablets, and non-nucleoside reverse transcriptase inhibitors (NNRTIs).**

If, upon review, it is determined that the clinical trial discussed in Item 13 below adequately addresses the potential interaction between artemether and lumefantrine and NNRTIs, then this *in vitro* study will not be needed. Otherwise, refer to the guidance for industry titled *Drug Interaction Studies--Study Design, Data Analysis, and Implications for Dosing and Labeling* for details on the conduct of the *in vitro* study.

The timetable you submitted on March 26, 2009 states that you will conduct this study according to the following timetable:

Final Protocol Submission:	by June 2011
Study Start Date:	by January 2012
Final Report Submission:	by January 2013

Finally, we have determined that only clinical trials (rather than an observational study) will be sufficient to assess the signal of serious risk of auditory dysfunction or identify an unexpected serious risk arising from treatment failure of Coartem Tablets due to altered metabolism by co-administered drugs or drug-drug interactions.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following clinical trials:

10. **Complete the currently ongoing trial "An open label, single center study of the effects of Coartem, Malarone and artesunate-mefloquine on auditory function following the treatment of acute uncomplicated *P. falciparum* malaria in patients 12 years of age or older in Columbia."**

The timetable you submitted on March 26, 2009 states that you will conduct this trial according to the following timetable:

Trial Start Date:	ongoing
Final Report Submission:	by March 2010

11. **Complete a clinical drug interaction trial to evaluate the effect of a co-administered CYP3A4 inducer on the pharmacokinetics of artemether and lumefantrine, the components of Coartem Tablets.**

Complete a clinical drug interaction trial using a potent CYP3A4 inducer, such as rifampin, to evaluate the effect of co-administering the inducer on the pharmacokinetics of artemether and lumefantrine. If, upon review, it is determined that the trial adequately addresses the potential interaction between artemether and lumefantrine and rifampin, then an *in vitro* study to characterize the potential interaction between artemether and lumefantrine and rifampin will not be needed (see Item 7 above).

The timetable you submitted on March 26, 2009 states that you will conduct this trial according to the following timetable:

Protocol Submission:	by June 2009
Trial Start Date:	ongoing
Final Report Submission:	by March 2011

12. **Complete a clinical drug interaction trial to evaluate the two-way interaction between artemether and lumefantrine, the components of Coartem Tablets, and a protease inhibitor (PI).**

Complete a clinical drug interaction trial using a representative PI, such as lopinavir/ritonavir or ritonavir, to evaluate the two-way interaction between artemether and lumefantrine and a PI. If, upon review, it is determined that the trial adequately addresses the potential interaction between artemether and lumefantrine and PIs, then an *in vitro* study to characterize the potential interaction between artemether and lumefantrine and a PI will not be needed (see Item 8 above).

The timetable you submitted on March 26, 2009 states that you will conduct this trial according to the following timetable:

Protocol Submission:	by June 2009
Trial Start Date:	ongoing
Final Report Submission:	by March 2011

13. **Complete a clinical trial to evaluate the two-way interaction between artemether and lumefantrine, the components of Coartem Tablets, and a non-nucleoside reverse transcriptase inhibitor (NNRTI).**

Complete a clinical drug interaction trial using a representative NNRTI, such as efavirenz or nevirapine, to evaluate the two-way interaction between artemether and lumefantrine and a NNRTI. If, upon review, it is determined the trial adequately addresses the potential interaction between artemether and lumefantrine and NNRTIs, then an *in vitro* study to characterize the potential interaction between artemether and lumefantrine and an NNRTI will not be needed (see Item 9 above).

The timetable you submitted on March 26, 2009 states that you will conduct this trial according to the following timetable:

Protocol Submission:	by June 2009
Trial Start Date:	ongoing
Final Report Submission:	by March 2011

14. **Conduct a clinical interaction trial to evaluate the induction potential of artemether and lumefantrine, the components of Coartem Tablets, on CYP3A4 substrates.**

If the results of the *in vitro* study (see Item 6 above) are positive, a clinical trial will be needed to further characterize the effect of artemether and lumefantrine on the pharmacokinetics of co-administered drugs that are metabolized by the CYP3A4 enzyme system, such as oral contraceptives.

The timetable you submitted on March 26, 2009 states that you will conduct this *in vivo* study, if needed, according to the following timetable:

Final Protocol Submission:	by June 2011
Trial Start Date:	by October 2011
Final Report Submission:	by October 2012

Submit the protocols to an IND with a cross-reference letter to NDA 22-268. [redacted]

Submit all final report(s) to your NDA 22-268. Use the following designators to prominently label all submissions, including supplements, relating to these postmarketing requirements as appropriate:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(o)**
- **Required Postmarketing Correspondence under 505(o)**

We request that you report to FDA the start date for each Postmarketing Requirement listed above. Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS

We remind you of your postmarketing commitment in your submission dated March 26, 2009. This commitment is listed below.

15. **Develop a dissolution test method for Coartem Tablets to achieve a minimum [redacted] dissolution of each component, artemether and lumefantrine.**

    Develop a test method to achieve [redacted] dissolution of each component in Coartem Tablets, artemether and lumefantrine, through the proposed shelf life. If possible, one dissolution test method should be developed for both components. Two yearly interim reports should also be submitted.

    The time table you submitted on March 26, 2009 states that you will conduct this study according to the following timetable:

Study Start:	by June 2009
Interim Report Submissions:	June 2010, June 2011
Final Report Submission:	by December 2011

We request that you report to FDA the start date of the Postmarketing Commitment listed above. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report and, for clinical trials, the number of patients entered into each trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **"Postmarketing Commitment Protocol,"** **"Postmarketing Commitment Final Report,"** or **"Postmarketing Commitment Correspondence."**

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

Please submit one market package of the drug product when it is available.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-1600.

Sincerely,

[See appended electronic signature page]

Edward Cox, M.D., M.P.H.
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Edward Cox
4/7/2009 06:33:23 PM

Appendix C

US005677331A

United States Patent [19]

Zhou et al.

[11] Patent Number: 5,677,331

[45] Date of Patent: Oct. 14, 1997

[54] ANTIMALARIAL COMPOSITIONS

[75] Inventors: **Yiqing Zhou; Dianxi Ning; Shufen Wang; Deben Ding; Guofu Li; Chengqi Shan; Guangyu Liu**, all of Beijing, China

[73] Assignees: **Ciba-Geigy AG**, Basel, Switzerland; **Institute of Microbiology and Epidemiology, Academy of Military Medical Sciences**, Beijing, China

[21] Appl. No.: **216,440**

[22] Filed: **Mar. 23, 1994**

Related U.S. Application Data

[63] Continuation of Ser. No. 43,998, Apr. 7, 1993, abandoned, which is a continuation of Ser. No. 714,229, Jun. 12, 1991, abandoned.

[30] **Foreign Application Priority Data**

Aug. 8, 1990 [CN] China 90106722.9
Apr. 24, 1991 [CN] China 91102575.8

[51] **Int. Cl.**[6] **A61K 31/335**; A61K 31/135

[52] **U.S. Cl.** **514/450**; 514/648; 514/895

[58] **Field of Search** 514/450, 648, 514/895

[56] **References Cited**

FOREIGN PATENT DOCUMENTS

0 362 810 4/1989 European Pat. Off. .

OTHER PUBLICATIONS

Deng, Chemical Abstracts, vol. 112, No. 7, Feb. 12, 1990 p. 1, Abstract No. 48094s.

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Who, "Practical Chemotherapy of Malaria", World Health Organization Technical Report Series 805 (1990).

Deng et al., Chemical Abstracts, vol. 114 p. 595 (1991), Abstract No. 6046p.

Wang et al., Chemical Abstracts, vol. 101, p. 385 (1984), Abstract No. 136941u.

CA 97(4): 28538h, Wang et al., 1982.

CA 113(5): 34389a, Sethi et al., 1988.

Merck Index, Therapeutic Catagory p. 16, 1989.

CA 103:134524, Lin et al., 1985.

Primary Examiner—Kimberly Jordan
Attorney, Agent, or Firm—Wenderoth, Lind & Ponack

[57] **ABSTRACT**

The invention relates to a synergistic antimalarial composition which comprises the antimalarial agent benflumetol and also an antimalarial agent from the artemisinine group such as artemether. The composition can be formulated into solid dosage forms such as tablets and is useful for the treatment of drug resistant malaria.

5 Claims, No Drawings

ANTIMALARIAL COMPOSITIONS

This application is a continuation of now abandoned application Ser. No. 08/043,998, filed Apr. 7, 1993, which is a continuation of now abandoned application Ser. No. 07/714,229, filed Jun. 12, 1991.

The present invention relates to a synergistic antimalarial composition, methods of treating malaria by administering that composition, and to a process for the preparation of that synergistic antimalarial composition.

Drug resistant malaria is a serious clinical and public health problem. The malaria parasite *Plasmodium falciparum* has developed the versatility of evading the effects of standard drugs such as chloroquine either by genetic mutation or by non-genetic adaption methods. The spread of *Plasmodium falciparum* resistant to chloroquine and other antimalarial drugs is a major challenge to health care programms in tropical and subtropical countries. Therefore, novel pharmaceutical compositions which diminish the resistance of malarial parasites, are needed for successful therapy.

The antimalarial effect of compositions containing the individual agent benflumetol has been reported in Chemical Abstracts 97:28538 h and 101:136941u. Other compositions contain combinations of known antimalarial agents. For example, the combination of amodiaquine and tetracycline have been used in the clinic [Suphat Noeypatimanond, et al. (1983), Treatment of *Plasmodium falciparum* malaria with a combination of amodiaquine and tetracycline in central Thailand, Trans. R. Soc. Trop. Med. and Hyg. 73 (3), 338–340]. Recently another antimalarial combination FANSIMED (mefloquine, pyrimethamine and sulphadoxine) is undergoing clinical trials [Tropical Diseases Research, Seventh Programme Report, Chapter 2; Malaria, UNDP World Bank/WHO. Published by WHO, 1985].

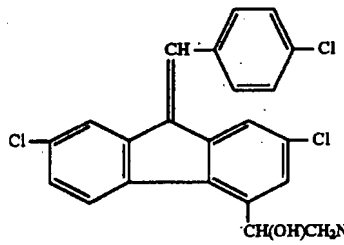
The use of combinations of artemisinine, its derivatives and other antimalarial compounds, such as quinine, has been proposed in the Indian Patent Application 26 BOM87 and the German Patent Application P 37 15 378. Also the synergistic effect of a combination of artemisinine and primaquine is known (Wan Yaode, Cang Qizhong, Pharmacy Bulletin, Vol. 16, No. 1, 1981).

Combinations of the antimalarial agents artemether, arteether, artemisinine, dihydroartemisinine, or artesunate with quinidine or with mefloquine have been disclosed in the European Patent Application 362 810.

Motivation for the present invention has been drawn from the need in therapy for an improved antimalarial composition of higher activity and lower resistance against malarial parasites such as *Plasmodium falciparum*.

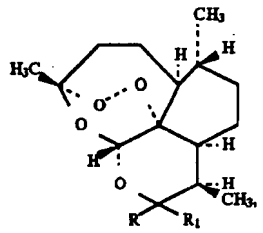
It has now been found that pharmaceutical compositions containing the active agent benflumetol in combination with the agent artemisinine or especially one of its derivatives such as artemether have excellent antimalarial activity and are more active than compositions containing only the individual component benflumetol, or alternatively, artemisinine derivatives.

The following invention relates to a pharmaceutical composition suitable for synergistic action of the active components against malaria comprising a synergistically effective amount of a compound of the formula:



(I)

combined with a synergistically effective amount of at least one compound of the formula:



(II)

wherein R and R_1 together represent oxygen or one of R and R_1 individually represents hydroxy, C_1–C_6-alkoxy, C_1–C_6-alkenyloxy, C_1–C_5-alkanoyloxy, carboxy-C_1–C_6-alkanoyloxy, cyclohexanecarbonyloxy, benzoyloxy or naphthoyloxy and the other represents hydrogen, or a pharmaceutically acceptable salt thereof and optionally pharmaceutically acceptable additives.

The general definitions and terms used in this specification of the invention preferably have the following meanings:

The term pharmaceutical composition defines a mixture comprising the compound of the formula I and at least one compound of the formula II. This mixture either consists of a dry preparation of the active components (I) and (II) such as a lyophilisate or preferably contains additives suitable for the manufacture of a dosage form such as tablets, capsules or suppositories.

The term synergistic action defines the increase of efficacy of the composition above the efficacy level of at least one individual active component at the given dose. Preferably, the efficacy of all active components present in the pharmaceutical composition is increased. The synergistic effect is most desirable as it enables the use of a lower dosage of an individual component and/or improvement of activity above the activity levels of the individual components.

The synergism of the claimed composition is proved by experimental results from in-vitro and in-vivo models. The results show that the activity of the component according to formula I is raised as compared to the activity of benflumetol (I) in an individual dosage form and that the activity of the component (II) such as artemether is also being raised.

Synergistic action against malaria of the composition according to the present invention permits the combined application of different drug regimens during therapy by the administration of one dosage form such as one or two tablets per day.

The application of a dosage form comprising the active component benflumetol (I) allows permanent action against malaria. The presence of the second active component (II) in the same dosage form such as artemether (one of R and R_1 represents hydrogen and the other represents methoxy) allows immediate and fast action against protozoa after the outbreak of the disease. This is evident from tests carried out in different standard in-vitro and in-vivo pharmacological models.

The active component (I), wherein Bu denotes n-butyl, is known under the name benflumetol, see C.A.R.N. 82186-77-4. Pharmaceutical compositions containing benflumetol individually and its activity against malaria are also known, see the abstracts according to C.A. 97:28538h and 101:136941. The preparation of benflumetol has been disclosed in the Published Chinese Patent Application 88/07666.X.

The active component (II) wherein R and R_1 together represent oxygen is known under the name artemisinine. The component (II) wherein one of R and R_1 represents hydrogen and the other represents hydroxy is named dihydroartemisinine.

In a compound of the formula II C_1–C_6-alkoxy preferably represents methoxy or ethoxy. The compound (II) wherein one of R and R_1 represents methoxy and the other represents hydrogen is known under the name artemether. The compound (II) wherein one of R and R_1 represents ethoxy and the other also represents hydrogen is known under the name arteether.

In a compound of the formula II C_1–C_6-alkenyloxy is preferably allyloxy. C_1–C_5-alkanoyloxy is preferably acetoxy or propionyloxy. Carboxy-C_1–C_6-alkanoyloxy is preferably carboxy-n-propionyloxy. The carboxy group may be present in salt form (carboxylate), e.g. as sodium or potassium salt. The compound (II) wherein one of R and R_1 represents sodium carboxylate-n-propionyloxy (—O—CO—CH_2—CH_2—CO_2—Na) and the other represents hydrogen is named artesunate.

The active components artemisinine, dihydroartemisinine, arteether and artesunate comprised by formula II are preferred. Especially preferred is artemether.

The generic names used in the specification of the present invention are taken from "Tropical Diseases Research, Seventh Programme Report", Chapter 2; Malaria, UNDP WORLD BANK/WHO, Published by WHO, 1985.

The active components (II) artemisinine, dihydroartemisinine, arteether, artemether and artesunate are known. Artemisinine has been isolated from *Artemisia annua* L. and subsequently synthesized. It has been used for the treatment of Falciparum malaria [H. P. Koch (1981) Qinghasosu: a potent antimalarial from plant origin, Pharmacy International (New Drugs), p. 184–185, Elsevier North Holland Biomedical Press; L. J. Bruce-Schwatt (1982), Qinghaosu: a new antimalarial, British Med. J., 184, 767–768]. The clinical evaluation of the activity of artemisinine in 2069 patients was reported by Koch in 1981, of which 1511 patients were treated for a vivax malaria [H. P. Koch (1981) Qinghaosu: a potent antimalarial from plant origin, Pharmacy International (New Drugs), p. 184–185, Elsevier North Holland Biomedical Press]. It has also been shown to be active against chloroquine-resistant strains of *Plasmodium falciparum* in man [J. P. Jiang et al. (1982), Antimalarial activity of mefloquine and qinghasosu. Lancet, ii. 8293, 185–287]. Dihydroartemisinine, arteether, artemether, artesunate are semi-synthetic derivatives of artemisinine. Their antimalarial activity is disclosed in different WHO reports. [WHO. Report of the Scientific Working Group on the Chemotherapy Malaria, TDR/Chemal 3rd Review, 85. 3, Geneva, 3–5. Jun. 1985 and the references contained therein].

Conventional pharmaceutically acceptable additives are preferably present in the composition according to the present invention. The additives are used for the preparation of enteral or parenteral dosage forms according to conventional formulation methods.

For oral administration suitable additives include inert diluents or fillers, thereby forming dosage forms such as tablets, powders, capsules, and the like. The pharmaceutical compositions can, if desired, contain additional ingredients such as flavourings, binders, excipients and the like.

For example, tablets containing various solid additives such as starch, dextrin, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard gelatin capsules, preferred materials therefore include lactose or milk sugar and high molecular weight polyethylene glycols.

For other oral dosage forms the mixture of the compounds can for example be administered in a gelatin capsule. Such formulation could be based on a suitable refined edible oil such as sunflower oil, corn oil, peanut oil, coconut oil or til oil.

In a preferred embodiment of the present invention, the active components (I) and (II) are formulated in a single unit dosage form such as tablets or capsules.

The active components (I) and (II) may also be formulated into two individual dosage forms contained within one administration system (kit of parts), which are simultaneously or consecutively administered. The same route of administration is possible, e.g. administration of two individual dosage forms contained within one kit of parts. One tablet or capsule containing component (I) and, consecutively, a second dosage form containing component (II) is administered. An individual dose regimen may be developed especially during clinical treatment, e.g. by administering after the first occurrence of malaria a tablet or capsule containing a high dose of the active component (II) or, correspondingly, multiplying lower doses in the beginning of malaria attacks, and administering also a tablet or capsule containing a lower dose of the active component (I). In the course of treatment, dosage forms containing a lower dose of component (II) are administered. Different dosage forms present in one kit-of-parts may also be administered simultaneously or consecutively, e.g. by administration of a tablet containing component (I) and a suppository containing component (II). The dosage range may also be varied according to the dose regimens given above.

The usefulness of the pharmaceutical composition according to the present invention in therapy against malaria is evident from in-vitro and in-vivo results from experiments carried out in established test models. Some results are given in the Examples. The ability of the composition to act as an effective and rapid acting antimalarial agent even against strains of *P. berghei* known to be extremely resistant against other antimalarial agents reflects the usefulness of the present invention.

The present invention also relates to a method of treatment against malaria which comprises administering to a patient after the outbreak of malaria the above-mentioned pharmaceutical composition comprising the combined active components (I) and (II). The composition is administered to the patient for a period of time of at least four days, preferably five or more days.

The term method of treatment also comprises prophylactic administration of the composition to healthy patients to prevent the outbreak of the disease in high-risk areas of contamination, especially in regions between the tropics of capricorn and cancer.

The dose of the active component benflumetol (I) as contained in the pharmaceutical composition may vary within wide limits and depends on the condition of the

patient and the time period elapsed after the outbreak of the disease. Based on in-vivo data from *P. berghei* model experiments with mice as reported below in the Examples, it is established that the daily dose of benflumetol is between about 0.2–5.0 mg/kg, preferably 0.2–10.0 mg/kg and especially about 0.2–5.0 mg/kg. This daily dose can be raised considerably upon need in view of the low toxicity and high tolerability of benflumetol. It is also estimated that the daily dose of component (II) in the composition, especially artemether, is between 0.2 and 5 mg/kg, preferably 0.3–3.0 mg/kg and especially between about 0.4–5.0 mg/kg.

The dose ratio of component (I) to component (II) may also vary within wide limits. It has been determined that synergism will be especially efficient if benflumetol is administered in equal weight amounts or, preferably, in excess amounts as compared to the weight amounts of component (II) administered. Accordingly, the weight amount of benflumetol may vary from one to ten parts for each part of component (II), especially artemether administered. Preferably, three to seven parts and especially five to six parts of benflumetol are administered for each part of component (II). The dose amounts given and dose ratios refer to daily administrations.

The invention also relates to a process for the preparation of the pharmaceutical composition suitable for synergistic action of the active components against malaria which comprises combining an effective amount of a compound of formula I with an effective amount of a compound of the formula II and formulating this combination of active components under optional addition of pharmaceutically acceptable additives to a suitable dosage form.

The novel pharmaceutical compositions contain, for example, from 10% to 80%, preferably from 20% to 60%, of the combination of active components. Pharmaceutical compositions according to the invention are suitable for enteral administration and are, for example, formulated into oral dosage unit forms, such as dragées, tablets, capsules or suppositories. These are manufactured in a manner known per se, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes. For example, pharmaceutical preparations for oral administration can be obtained by combining the active ingredient with solid carriers, optionally granulating a resulting mixture, and processing the mixture or granulate, if desired or necessary, after the addition of suitable adjuncts, to form tablets or dragée cores.

In a preferred embodiment of the process, the active components (I) and (II) are milled either individually or together to particle sizes from about 10μ to about 400μ, preferably 20μ to 200μ. At least 90% of the crystals of the active components are present in these ranges.

Particles of this size are obtained by conventional comminution methods, e.g. grinding in an air jet mill, ball mill or vibrator mill. Micronisation is preferably effected by per se by known methods using an ultrasonics disintegrator, e.g. of the Branson Sonifier type as described e.g. in J. Pharm. Sci. 53 (9), 1040–1045 (1965), or by stirring a suspension with a high-speed agitator, for example with a stirrer of the Homorex type (supplied by Brogli & Co., Basel). In these preferred methods, micronisation is effected at about 500 to 10,000 rpm by dissolving or suspending the combination of active components in an organic solvent, e.g. methanol, ethanol or propylene glycol, and precipitating it in microcrystalline form at ca. 0°–5° C. in water or an aqueous salt solution, e.g. 2% sodium chloride solution which may additionally contain a protective colloid such as gelatin or a cellulose ether, e.g. methyl cellulose or hydroxypropyl methyl cellulose, in low concentration (0.1–1%), and filtering the resultant stirred suspension. The filter cake is dried at low temperature, e.g. ca. 0°–5° C., under vacuum (e.g. below 50 mbar, preferably at 0.5 mbar). The subsequent drying can be effected at ca. 50°–90° C.

The crystals thus obtained are then formulated to granulates, preferably by wet granulation which is carried out according to standard methods.

The pharmaceutical composition is preferably prepared by compressing a granular formulation which is obtained, for example, by sieving and, if desired, by comminuting the drug, with or without the excipients, compacting with another solvent such as ethanol or water, removing the solvent or drying, with or without the addition of lubricants or glidants such as magnesium stearate or TWEEN, comminuting the granules and sieving once more.

The granules can be compressed to tablet cores in a conventional tabletting machine, for example an EKO Korsch eccentric tabletting machine, at a pressure of ca. 10 kN. Coating can be effected by applying an aqueous-ethanolic solution in which, for example, polyethylene glycol and saccharose is dissolved or dispersed.

Dragée cores are provided with suitable coatings that may be resistant to gastric juices, there being used, inter alia, concentrated sugar solutions that may contain gum arabic, talc, polyvinylpyrrolidone or polyethylene glycol. Colorings or pigments may be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of the active ingredient.

Further orally administrable pharmaceutical compositions are dry-filled capsules consisting of gelatin, and also soft sealed capsules consisting of gelatin and plasticiser, such as glycerine or sorbitol. The dry-filled capsules may contain the active components in the form of a granulate, for example in admixture with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and optionally stabilisers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, to which stabilisers may also be added.

Suitable for enteral administration are also suppositories that consist of a combination of the active ingredient and a suppository base. Suitable as suppository bases are, for example, natural or synthetic triglycerides, paraffins, polyethylene glycols or higher alkanols. It is also possible to use gelatin rectal capsules that contain a combination of the active ingredient and a base material; suitable base materials are, for example, liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

The following Examples illustrate the invention described above; they are not, however, intended to limit the scope of the invention in any way.

EXAMPLE 1

Determination of dose ratios for the combination of benflumetol with artemether:

Albino mice were infected with *Plasmodium berghei* as test strain. By using orthogonal design, parallel contrast experiments were carried out for different doses of the combination according to the "4-day inhibition test" method. ED_{50} or ED_{90} and the synergistic indices were calculated by means of a linear regression equation.

$$\text{Index of synergism} = \frac{ED_{50} \text{ or } ED_{90} \text{ for individual component}}{ED_{50} \text{ or } ED_{90} \text{ for that component in combination}}$$

Using this equation, the optimal weight ratio of drugs in this combination against murine malaria is calculated to be 2:0.75 (the index synergism for ED90>6). Based on experiments in murine malaria, experiments in rhesus monkey with *Plasmodium Knowlesi* were performed and the result showed that the optimal weight ratio of drugs in this combination against malaria is 3–6 parts of benflumetol to each part of artemether.

EXAMPLE 2

The synergism between the components benflumetol and artemether is determined according to the method of Peters: Am. Trop. Med. Parasitol Vol. 62, pg. 488–492 (1968). The results are reported in the following Table:

Blood schizintocidal action of artemether (A) and benflumetol (B) administered orally in varying proportions to mice infected with *P. Berghei* K_{173} N-strain in "4-day test" according to Peters (Mean values of three experiments)

Drug and dose	Effective dose of first component (mg/kg/day)	
(mg/kg/day)	ED_{50}	ED_{90}
Benflumetol (B)	1.30	2.70
+A 0.25	0.84	1.84
+A 0.50	0.78	1.57
+A 1.00	0.51	1.16
+A 2.00	0.16	0.57
+A 4.00	0.06	0.29
Artemether (A)	2.00	5.30
+B 0.37	1.49	4.46
+B 0.50	0.87	2.67
+B 0.75	0.93	3.44
+B 1.00	0.37	1.21
+B 1.50	0.25	0.83

All points representing ED_{50} and ED_{90} of the components A and B present in the combination being located beneath the addition indicate synergism between the individual components.

EXAMPLE 3

The rate of killing protozoa was determined in-vivo. When the protozoa concentration in the blood of mice increased to high density, a multiple dose equivalent, i.e. 20× ED_{90} was given intragastrically. The rate of decrease of protozoae in blood was observed uninterruptedly after administration. The timespan required for 90% decrease of the protozoae was 49.7 hours for the combination and 64.3 hours for benflumetol alone. Artemether alone could not kill protozoae by more than 90% before their number increased again.

EXAMPLE 4

Clinical determination of the best ratio of dose combination between artemether and benflumetol in the combination:

Based on the result of animal experiment with reference to the clinical effective doses of artemether and benflumetol singly, the optimal ratio of dose combination of these two components was calculated to be from 1:4 to 1:6. For example when 1:6 is chosen, the doses of artemether and benflumetol in each tablet would be 20 mg and 120 mg respectively. Two groups of patients given the combination with 1:5 and 1:6 ratios were selected for clinical parallel comparison trials. In both groups, the "3 days and 4 doses" treatment scheme was adopted, i.e. 4 tablets were administered at the first time and then 4 tablets each for three more times with 8, 24 and 48 hour intervals. That made altogether 16 tablets for each adult. 40 cases of pernicious malaria were selected and divided randomly into two groups. The following parameters were determined in these two groups after administration: 1) rate for decrease of protozoae at 24 hours; 2) average time for disappearance of protozoae; 3) average time for subsidence of fever; 4) 28-day cure rate.

The results showed that at 24 hours after administration the rates of decrease in protozoa in these two groups were 96.3% and 94.2%, the time periods for disappearance of protozoae were 34.8 hours and 36.0 hours and the average time periods for subsidence of fever were 23.2 hours and 22.4 hours respectively. However, the recrudescence rate on the 28lth day in the 1:5 group was 20% as compared to 0% in the 1:6 group (i.e. all of the patients in this group were cured). These results indicate that the optimum ratio of combination of artemether and benflumetol in the combination for treatment of human malaria is 1:6.

EXAMPLE 5

Toxicological Evaluation of the artemether-benflumetol combination:

The ratio of combination of 1:6 for artemether and benflumetol was used in these experiments. The medium lethal dose (LD50) for albino mice was found in acute toxicity experiments to be 4555 mg/kg for oral administration. Based on grading criteria for chemical toxicity, this complex prescription is of low grade of toxicity. Toxicity experiments for 14 days were performed in rats and beagles, which were divided into high-, medium- and low-dose groups. Drugs were administered per os once every day for successive 14 days. Appetite and body weight were observed, hematological and biological parameters were determined, and pathological examinations were made in major viscera and target organs of the drugs. The results revealed that the basic safety dose in rats was being equivalent from 40-fold to 50-fold of the dose administered to humans. Although some abnormal changes were found in target organs (liver and kidney)in higher dose groups, they recovered to normal on day 28 after administering the last dose. These results indicated that the toxicity of the synergistic combination is low, and the safety range is wide and free from irreversible toxic reactions.

EXAMPLE 6

Determination of therapeutic effect of individual components as compared to synergistic combination:

Two groups of patients were selected for oral administration and the 3 days and 4 doses treatment scheme. There were 20 patients with pernicious malaria in each group. The therapeutic effect of the combination and artemether and benflumetol singly were compared separately. The doses of both drugs in individual administration were about the same as in the complex prescription. The parameters determined were: 1) the rate for decrease of protozoa at 24 h post administrationem; 2) average time for disappearance of protozoae; 3) average time for fever subsidence; and 4) cure rate at the 28th day.

The rates of decrease in protozoae at 24 hours after administration were found to be 97%, 95.1% and 74.5% for

the combination, individual artemether, and individual benflumetol respectively. The times for disappearance of protozoae were 35.6 h, 38.7 h and 68.4 h respectively. The average time for fever subsidence was 23.8 h, 19.7 h and 40 h and the 28-day cure rates were 95%, 45% and 65% respectively. This experimental therapeutic scheme indicated clearly the superiority in therapeutic effect of the combination over the individual drugs.

EXAMPLE 7

Additional clinical trials for the combination artemether/benflumetol:

a) With the 3 days and 4 doses schemes and oral administration, altogether 400 patients with pernicious malaria were treated. Main parameters observed were: 1) average time period for disappearance of protozoae (the results were 23.2–41.0); 2) average time period for subsidence of fever (20.4–25.7); 3) 28-day cure rate (average 96.8%).

b) The combination composition was also administered with the 3 days and 4 doses treatment scheme, i.e. 4 tablets the first time and then 4 tablets each time at 8, 24 and 48 h with a total of 16 tablets for adults. 48 vivax malaria patients were treated with the combination. The parameter observed were 1) average time for disappearance of protozoa (the results were 22.8±9.5 h) average time for subsidence of fever (13.6±6.9 h); 3) 28-day cure rate (91.67%). These results demonstrated remarkable therapeutic effect of the combination against vivax malaria.

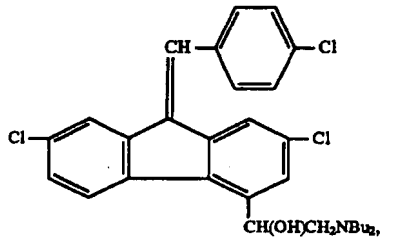
EXAMPLE 8

Preparation of Tablets.
benflumetol 120 mg
artemether 20 mg
corn starch 100 mg
dextrin 40 mg
Tween®-80 0,6 mg
15% paste of corn starch "sufficient"
Mg-stearate 3 mg

Artemether crystals are passed trough a 100 mesh size sieve. Benflumetol crystals are passed through a 60 mesh size sieve and mixed with the artemether solid, starch and dextrin. This mixture is passed 3 times through a 40 mesh size sieve. Tween®-80 is added to the paste of starch which is mixed with the above formulation. This mixture is granulated by way of wet-granulation, passed through a 40 mesh size sieve, dried at reduced pressure at 50°–60° C.. The Mg-stearate is added, and the tablets are pressed.

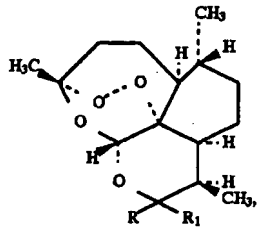
We claim:

1. A pharmaceutical composition to be administered orally to humans, suitable for synergistic action of the combined active components against malaria, which composition consists of a synergistic antimalarially effective amount of a combination of the compound benflumetol of the formula:



(I)

in fixed combination with the compound artemether of the formula:



(II)

wherein one of R and R_1 individually represents methoxy, and the other represents hydrogen,
and pharmaceutically acceptable additives.

2. A pharmaceutical composition according to claim 1, which composition consists of a synergistically effective amount of one to ten parts by weight of benflumetol (I) for each part by weight of artemether (II).

3. A pharmaceutical composition according to claim 1, which composition consists of a synergistically effective amount of three to seven parts by weight of benflumetol (I) for each part by weight of artemether (II).

4. A pharmaceutical composition according to claim 1 which composition consists of a synergistically effective amount of five to six parts by weight of benflumetol (I) for each part by weight of artemether (II).

5. A method of treating malaria which comprises administering orally to a human in need of such treatment a synergistic antimalarially effective amount of a combination of benflumetol of formula (I) and artemether of formula (II).

* * * * *

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NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER NJ 07936-1080

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

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Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA.22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,677,331	**$850.00**	**$0.00**	**04/02/01**	**08/216,440**	**10/14/97**	**03/23/94**	**04**	**NO**	**418634ACCNCO**

UNITED STATES PATENT AND TRADEMARK OFFICE

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5,677,331	**$2,300.00**	**$0.00**	**04/01/05**	**08/216,440**	**10/14/97**	**03/23/94**	**08**	**NO**	**418634ACCNCO**

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Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,677,331	**$4,110.00**	**$0.00**	**03/18/09**	**08/216,440**	**10/14/97**	**03/23/94**	**12**	**NO**	**INST OF MICROBIOLOGY & EP**

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DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Promotional

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
05/26/2009				

Description :

PEP, COR-900123 Table Top panel #1. PEP, COR-900123-A Table Top Panel #2. PEP, COR-900123-B Table Top Panel #3

URL:

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NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Promotional

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
04/30/2009				

Description :

PLT, COR-400001 Coartem Announcement Letter for Wholesalers . (PS)
URL:

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NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Labeling

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
04/23/2009				

Description :

Final printed container label as requested in approval letter dated April 7, 2009 (ESG).
URL:

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NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Labeling

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
04/22/2009				

Description :

Final Printed labeling in SPL format as requested in the approval letter dated April 7, 2009 (ESG).
URL:

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NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
04/10/2009				

Description :

Request to waive the requirement to submit Form 3500A for adverse experiences determined to be both non-serious and labeled in the periodic safety report (PS).
URL:

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NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Approve	Supplement Number
04/07/2009				

Description :

FDA LETTER approving the new drug application submitted on June 27, 2008. This NDA provides for the use of Coartem Tablets for the treatment of acute , uncomplicated malaria infections due to Plasmodium falciparum in patients of 5kg bodyweight and above . It should be noted that the original NDA was separated into two NDAs for administrative purposes . The other NDA number is 22-538.
URL:

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NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
FDA/Novartis Meeting Minutes

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
04/06/2009				

Description :

FDA minutes of Teleconference held on December 17, 2008 to discuss concerns regarding manufacturing facilities inspections .
URL:

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NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
FDA/Novartis Meeting Minutes

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
04/06/2009				

Description :

FDA minutes of Teleconference held on December 22, 2008 to follow up on previous telecon and clarify concerns regarding manufacturing facilities inspections .
URL:

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NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
FDA/Novartis Meeting Minutes

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
03/30/2009				

Description :

FDA Minutes of the February 6, 2009 Telecon to discuss concerns related to a recently published paper discussing the efficacy of Coartem in pregnant women and current and ongoing studies examining the effects of primaquine and Coartem used in combination .
URL:

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Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
03/26/2009				

Description :

Response to FDA request dated March 24, 2009 for Postmarketing Requirments 1-14 and Commitment 15 as agreed (ESG).
URL:

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Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
FDA/Novartis Meeting Minutes

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
03/23/2009				

Description :

FDA Minutes of the February 26, 2009 teleconference to discuss spectral characterization of impurities and the dissolution procedures and acceptance criteria for the drug substance .
URL:

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NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
CMC

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
03/18/2009				

Description :

Response to FDA fax request received March 17, 2009 for CMC information (ESG).
URL:

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NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
CMC

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
03/11/2009				

Description :

Response to FDA Request from ONDQA regarding CMC information dated March 5, 2009 (ES).
URL:

Read Attachments

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NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
CMC

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
03/09/2009				

Description :

Response to FDA request received February 26, 2009 for copies of IR and NMR scans of impurity peak noted in some drug substance Artemether samples (ESG).
URL:

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NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
FDA/Novartis Meeting Minutes

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
03/09/2009				

Description :

FDA meeting minutes of the teleconference between Novartis and the FDA on December 12, 2008 (ES)
URL:

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NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
FDA/Novartis Meeting Minutes

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
03/09/2009				

Description :

FDA meeting minutes pertaining to teleconference of October 21, 2008 to discuss question #13 from an Office of New Drug Quality Assessment ., (ONDQA) information request dated , October 9, 2008 (ES)
URL:

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NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
FDA/Novartis Meeting Minutes

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
03/04/2009				

Description :

FDA teleconference minutes from meeting held on October 30, 2008 to discuss ONDQA requests dated October 9 and 28, 2008.
URL:

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NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
FDA/Novartis Meeting Minutes

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
03/04/2009				

Description :

FDA Meeting Minutes from teleconference of December 2, 2008 to discuss a November 26, 2008, Office of New Drug Quality Assurance information request (ES)
URL:

Read Attachments

NOVARTIS

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NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
FDA/Novartis Meeting Minutes

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
02/27/2009				

Description :

FDA official meeting minutes of telecon held on October 1, 2008 to clarify preclinical tables requested in 74-Day Filing Letter .
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
FDA/Novartis Meeting Minutes

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
02/27/2009				

Description :

FDA official meeting minutes of telecon held on October 28, 2008 to clarify impurity levels in tablets for preclinical studies submitted on October 8, 2008.
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
FDA/Novartis Meeting Minutes

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
02/26/2009				

Description :

FDA official telecon meeting minutes from meeting held on October 15, 2008. The purpose of the meeting was to provide advice on Novartis December 3, 2008 Advisory Committee Meeting Presentation for NDA 22-268. (PS)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
FDA/Novartis Meeting Minutes

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
02/26/2009				

Description :

FDA official meeting minutes of telecon held on October 15, 2008 to discuss December 3, 2008 Advisory Committee Meeting Presentation for NDA 22-268.
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
CMC

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
02/26/2009				

Description :

TELECON with FDA to discuss the Coartem NDA with a follow -up on open CMC items that were sent on February 23, 2009.

URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
FDA/Novartis Meeting Minutes

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
02/25/2009				

Description :

FDA official meeting minutes of telecon held on July 8, 2008 to discuss DSPTP to further clarify to Novartis the specific types of subject records that need to be identified at clinical sites to be inspected by Division of Scientific Investigation (DSI).
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
FDA/Novartis Meeting Minutes

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
02/25/2009				

Description :

FDA official meeting minutes of telecon held on July 25, 2008 to discuss clarification of materials to be submitted for determination of a Priority Review Classification for NDA 22-268.
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
FDA/Novartis Meeting Minutes

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
02/25/2009				

Description :

FDA official meeting minutes of telecon held on July 28, 2008 to discuss Priority Review Teleconference Follow Up

URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
FDA/Novartis Meeting Minutes

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
02/25/2009				

Description :

FDA official meeting minutes of telecon held on August 13, 2008 to discuss DSPTP 's Concerns with information requests being delayed, incomplete submissions, and Applicant NDA management .
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
FDA/Novartis Meeting Minutes

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
02/25/2009				

Description :

FDA official meeting minutes of telecon held on September 23, 2008 to discuss DSPTP and Division of Scientific Investigation (DSI) ongoing obstacles to scheduling FDA inspections at Chinese and Thailand clinical sites and Novartis Headquarters .
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
FDA/Novartis Meeting Minutes

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
02/25/2009				

Description :

FDA official meeting minutes of telecon held on November 7, 2008 to clarify why the Division of Scientific Investigation (DSI) requested a teleconference on November 12, 2008.

URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
FDA/Novartis Meeting Minutes

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
02/25/2009				

Description :

FDA official meeting minutes of telecon held on November 12, 2008 to discuss with DSPTP and Division of Scientific Investigation (DSI) the concerns regarding procedures involving the inspection at Novartis Headquarters in Basel , Switzerland .
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
FDA/Novartis Meeting Minutes

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
02/25/2009				

Description :

FDA official meeting minutes of telecon held on November 25, 2008 to discuss Novartis concerns that foreign staff will not be able to attend December 3, 2008 Advisory Committee Meeting .

URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
FDA/Novartis Meeting Minutes

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
02/20/2009				

Description :

FDA Minutes of the January 30, 2009 Telecon to discuss outstanding Pharmacology / Toxicology concerns that were sent via email on January 23, 2009.
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
02/19/2009				

Description :

Respone to FDA Regarding QTC Prolongation . Novartis agrees with FDA that all statements on restrictions of the use of primaquine in the label should be removed (ESG).
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
02/13/2009				

Description :

Response to FDA Request Regarding Articles Discussed in Telecon on Jan 30, 2009 (ESG).
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
02/12/2009				

Description :

Protocol submission for Study CCOA 566A2417 and Amendment 1 as discussed during Postmarketing Requirements (ESG).

URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
CMC

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
12/22/2008				

Description :

Response to December 11, 2008 FDA request and disintegration method proposal , in fulfillment of made in Novartis' November 6, 2008 response to FDA's October 9, 2008 request (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
12/22/2008				

Description :

Response to FDA fax request of December 11, 2008 regarding study numbers for pediatric patient (s) as young as 2 months of age (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
12/18/2008				

Description :

Response to Clinical Information Request dated December 2, 2008 (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
12/18/2008			Other	

Description :

Email correspondence from FDA advising that Dr . Pagay has been asked to address Novartis' concern regarding the expiration on the HDPE bottles (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
12/17/2008				

Description :

Response to Statistics Information Request of December 12, 2008 regarding excluded subjects (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
12/15/2008				

Description :

Email correspondence providing feedback on items stemming from December 2, 2008 telecon with FDA (ES)

URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
12/12/2008				

Description :

Response to Information Request dated December 5, 2008 regarding parasite count results (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
12/12/2008				

Description :

Email correspondence providing feedback on question 3, stemming from December 2, 2008 telecon with FDA (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
12/10/2008				

Description :

Email correspondence providing details on Novartis' commitment to provide tablet disintegration method consistent with USP <701>, as requested in the FDA questions dated 9-Oct-2008 (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
12/09/2008				

Description :

Response to FDA fax request of December 05, 2008 pertaining to Clinical and Statistical data (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
12/05/2008				

Description :

Email correspondence advising the agency that the =CMC response was sent to FDA on December 4, 2008. Courtesy copies of the cover letter and response is appended (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
CMC

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
12/04/2008				

Description :

Complete response to FDA request of November 26, 2008 and product stability data for drug product packaged in the proposed US configuration , HDPE bottles with child resistant closure ; as previously submitted on September 19, 2008. (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
12/03/2008				

Description :

Email to agency providing clarification to question by Dr . Matecka regarding HPLC (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type : Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
12/01/2008				

Description :

Response to FDA request of November 25, 2008 regarding Study A 030 (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
12/01/2008				

Description :

Email correspondence providing the Agency with informal response to CMC fax of November 26, 2008 (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
CMC

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
11/26/2008				

Description :

FDA Letter requesting regarding CMC information .
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
11/25/2008				

Description :

Response to FDA request for information dated November 20, 2008, surrounding subjects in study 2401 (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
11/25/2008				

Description :

Request for Priority Review Voucher following the approval of the marketing application for Coartem (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
CMC

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
11/25/2008				

Description :

Submission of recommendation for dissolution specifications suitable for release and shelf life to 36 months, taking into account the USP and available product data at several storage conditions ; which fulfils Novartis' commitment made in November 5, 2008 response to FDA (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
CMC

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
11/24/2008				

Description :

Email correspondence seeking CMC information to be submitted by December 1, 2008 (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
11/21/2008				

Description :

Response to FDA request of November 18 and 19, 2008, regarding parasite clearance times for Study 026 (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
11/20/2008				

Description :

Reponse to FDA fax request of November 12, 2008 regarding four points on which the Agency has asked for additional information . The purpose of this submission is to provide responses to items #1 and #4. Item # 2 will be addressed at the December 3, 200 Advisory Committee Meeting and response to Item #3 was submitted on November , 17, 2008 (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
11/17/2008				

Description :

Response to FDA fax request of October 10, 2008 regarding Maternal Health . Novartis is providing a formal response to point 2 of request; no information is provided for points #1 and #3, as no pregnancy registry has been developed during the Coartem program (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
11/17/2008				

Description :

Response to FDA fax of October 20, 2008, regarding the agency's notation that 2401 two different formulations were used in Study 2401 (ESG)

URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
General Correspondence

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
11/11/2008				

Description :

General correspondence providing list of Presenters , Consultants , Investigators and Sub - Investigators in preparation for the December 3, 2008 FDA Anti-Infective Advisory Committee Meeting (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Information	Supplement Number
11/07/2008				

Description :

Email correspondence following up on status of raw data for Parasite Clearance Time (PCT) for study 026 (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Information	Supplement Number
11/07/2008				

Description :

Follow-up email correspondence regarding PCT for study 026. Novartis also confirms that only formulation F 4 was used in study A 2401 (ES)

URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Information	Supplement Number
11/07/2008				

Description :

Email correspondence to the FDA seeking clarification pertaining to FDA 's fax request of October 10, 2008; which pertains to pregnancy registry and birth defects (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
CMC

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
11/06/2008				

Description :

Reponses to FDA requests of October 9, 2008 concerning the proposed drug substances and drug product and October 23, 2008, which requested stability data from proposed drug substance supplier ZMC. Question 12 of the former request was provided to the A agency on October 31, 2008 (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Information	Supplement Number
11/06/2008				

Description :

Email correspondence from FDA seeking clarification on the use of two formulations for study 2401, as referenced in F.4 and F.5. FDA's review team still requests the complete responses to those questions presented in the October 20, 2008 facsimile request (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
CMC

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
11/05/2008				

Description :

Complete response to FDA's October 28, 2008 request for information concerning the proposed drug substances Artemether and Lumefantrine and drug product , Coartem tablets (ESG)

URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
11/05/2008				

Description :

Response to FDA request for information as requested by Pharmacology Toxicology reviewer ; seeking_direction_as_to_the_studies_that_support_the_proposed_acceptance_criteria . . (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
11/05/2008				

Description :

Response to FDA request for clarification dated October 31, 2008; requesting details as to mechanism that would prevent a retail pharmacy from ordering and stocking COARTEM® (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
CMC

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
10/31/2008				

Description :

In response to FDA request for CMC information (Question 12) dated October 9, 2008 (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Labeling

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
10/31/2008				

Description :

In response to FDA fax request of October 17, 2008 where was asked to respond to a July 9, 2008 request to provide a more detailed annotation to the microbiology sections (12.1 and 12.2) of the proposed label for Coartem (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
10/30/2008				

Description :

Submission of Briefing Book in preparation for the December 3, 2008 FDA Anti-Infective Advisory Committee Meeting for NDA 022-268 Coartem (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Safety Report

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
10/28/2008				

Description :

Submission of four month (120-Day) Safety Update (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Information	Supplement Number
10/23/2008				

Description :

Email correspondence regarding telecon pertaining to drug product stability from supplier ZMC (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
CMC

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
10/23/2008				

Description :

FDA email correspondence requesting that Novartis provide "The stability data for artemether drug substance manufactured at the ZMC facility" (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Information	Supplement Number
10/16/2008				

Description :

Response to FDA fax request dated September 16, 2008, requesting additional clinical pharmacology information (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
10/13/2008				

Description :

In response to FDA email request of October 7, 2008 for Investigator Brochure (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
10/10/2008				

Description :

FDA fax requesting information on pregnancy registry and birth defects . Information was informally requested in an email dated October 8, 2008 (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
CMC

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
10/08/2008				

Description :

Complete response to CMC request as per telecon between Novartis , Dr. McMaster and Mr . DiBernardo of the Agency on October 1, 2008 (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
10/06/2008				

Description :

Submission of briefing book in support of October 16, 2008 Advisory Committee Preparation Meeting (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
10/01/2008				

Description :

In response to FDA email request of September 23, 2008 regarding study 028 (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
10/01/2008				

Description :

In response to FDA fax request of September 12, 2008 requesting that Novartis provide a data analysis report with interpretation comparing human and dog pharmacokinetics of artemether (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Information	Supplement Number
09/22/2008				

Description :

Email correspondence advising FDA that the stability update was sent through the gateway on September 19, 2008. The receipts for the aforementioned submission and September 15, 2008 CMC response are enclosed (PS)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
CMC

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
09/19/2008				

Description :

Submission of 9 month stability update for Coartem tablets drug product packaged in HDPE bottles with child-resistant closures as agreed upon at the Novemeber 9, 2007 pre-NDA meeting (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
09/17/2008				

Description :

In reponse to FDA request for information dated September 8, 2008 (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
09/12/2008				

Description :

In response to FDA fax request dated dated September 12, 2009. Novartis is submitting a response regarding Document # 51 (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Labeling

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
09/12/2008				

Description :

Response to Question 3 of FDA fax request of 28-Aug-2008. Novartis is providing sample packaging as requested (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
09/11/2008				

Description :

Response to FDA request for information as per fax dated July 9, 2008, requesting additional Microbiology information . Novartis is providing the PCR gel results for Study 028 from Thailand and advises the agency that Study A 2403 from the Swiss Tropical Institute cannot be located (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
09/10/2008				

Description :

Response to FDA fax request of August 19, 2008, requesting additional clinical information . Novartis is providing complete responses in regards to the worldwide post marketing safety data and coding dictionary (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
09/09/2008				

Description :

Response to FDA fax request for information dated August 29, 2008; requesting additional statistics information for your review (ESG)

URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
09/09/2008				

Description :

Response to FDA fax requested dated August 15, 2008, requesting additional clinical information for the Clinical Review team (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Information	Supplement Number
09/08/2008				

Description :

FDA letter communicating potential review issues (PS)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
09/05/2008				

Description :

Response to FDA request for information regarding mixed infections ; as requested during the July 25, 2008 teleconference (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
09/04/2008				

Description :

In response to FDA request of July 9, 2008, requesting additional Microbiology information (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
CMC

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
08/28/2008				

Description :

In response to FDA fax request for CMC information on August 14, 2008 (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Information	Supplement Number
08/28/2008				

Description :

Email correspondence to FDA advising that Novartis' response to FDA's CMC questions received by fax on August 14, 2008, has been sent electronically via the FDA gateway (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
08/22/2008				

Description :

Response to FDA clinical request of August 7, 2008 Novartis is currently responding to Items 2 and 3, which completes the response to FDA's August 7, 2008 facsimile (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
08/21/2008				

Description :

In response to FDA request of August 7, 2008 clinical request for information sent by facsimile ;
Novartis is responding to Item 4 (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
08/21/2008				

Description :

FDA letter advising Novartis that the agency is in the process of developing agenda for Anti -Infective Drugs Advisory Committee (AIDAC), which will be held tentatively on December 3, 2008 and Novartis will be advised of the meeting location once it has been confirmed (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riam,et®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
08/21/2008				

Description :

Novartis request for clarification in regards to clinical overview addendum on mixed infections (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
08/21/2008				

Description :

FDA email correspondence affirming that the October 3, 2008 and October 10, 2008 dates for the submission of a near Final version of the Briefing Package and Presentation Slides is acceptable to the agency (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
08/20/2008				

Description :

FDA email communicating that the agency would like to use the 16 years of age and younger as the cut off for children (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
08/19/2008				

Description :

In response to FDA fax request dated July 9, 2008, requesting additional Microbiology information (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
08/15/2008				

Description :

Submission of clinical pharmacology data in reponse to FDA fax request regarding exposure-response analyses (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
08/15/2008				

Description :

In response to FDA fax request dated August 7, 2008, requesting additional statistical information (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
08/15/2008				

Description :

In reponse to FDA fax request of July 29, 2008 requesting additional clinical information (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
08/08/2008				

Description :

In response to FDA request from teleconference of July 8, 2008 for Study 025/Site 3 and Study 026/Site 2 listing of available and unavailable inspections documents (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Request	Supplement Number
08/07/2008				

Description :

In reponse to FDA request for updated site information made on July 21, 2008 (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Request	Supplement Number
08/07/2008				

Description :

FDA fax request for information from the agency's Clinical team . FDA requests that the response be submitted as an official amendment to the NDA (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
08/05/2008				

Description :

In response to FDA request from July 25, 2008 teleconference ; Novartis is providing supportive data and discussion of the use of Coartem in the pediatric population (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Memo of Record (telephone report)

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
07/28/2008				

Description :

FDA telephone contact report for follow -up telecon regarding priority review . FDA agrees that correlating parasite clearance with fever reduction could strengthen argument for priority review (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
07/25/2008				

Description :

Email correspondence in response to FDA query regarding the location of CRFs that cover serious event for the key clinical studies (ES)

URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Memo of Record (telephone report)

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
07/25/2008				

Description :

FDA contact report for telecon on July 25, 2008 initiated by FDA to discuss their review of the Coartem NDA to determine priority review (ES)

URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
07/24/2008				

Description :

Request for five year exclusivity , with reference to Patent information , which was provided in this NDA in a submission dated June 27, 2008 (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
07/23/2008				

Description :

Submission of additional data in response to June 23, 2QOS request for QT -IRT consult (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
07/22/2008				

Description :

Submission of form 3674, which was inadvertently omitted from Novartis ' presubmission dated June 26, 2008 (ESG)

URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
07/22/2008				

Description :

Email correspondence providing the contact information for the six sites requested by the agency .
Formal filing will be made to the NDA (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Request	Supplement Number
07/21/2008				

Description :

FDA email requesting the complete address of CRO who is holding the site and subject records for Study 025 and 026 at Center 01 (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
07/21/2008				

Description :

Email correspondence to FDA providing gateway receipts related to Novartis response to FDA request to overall TOC and English -language labels (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Request	Supplement Number
07/21/2008				

Description :

FDA email requesting various investigators contact information (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Labeling
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
07/21/2008				

Description :

In response to FDA request of July 8, 2008 Novartis is submission the Overall NDA Table of Contents and all approved English language labels (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
07/17/2008			Other	

Description :

Email correspondence to FDA providing overall NDA table of contents requested via July 8, 2008 teleconference and labels for Coartem /Riamet from Australia , Switzerland (translated from German), and the UK. I also include the International Package Leaflet (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
07/17/2008				

Description :

In response to FDA request for information , made on July 2, 2008, seeking clarification on Novartis' request for NDA priority review (ESG)

URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Request	Supplement Number
07/16/2008				

Description :

Email correspondence to FDA providing response document and supporting information to your July 2 request for additional information in support of the argument for a priority review of the Coartem NDA (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
07/15/2008				

Description :

Submission or revised NDA form 356 for Novartis' submission of June 27, 2008, to correct for some information that was either incorrect or omitted (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Acknowledge	Supplement Number
07/14/2008				

Description :

FDA letter providing receipt acknowledgement for new drug application submitted on June 27, 2008 and received by the agency on June 27, 2008 (ES)

URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Request	Supplement Number
07/14/2008				

Description :

FDA email advising that FDA would like to have requested information for in support of the Priority review by on July 16th, 2008 (PS)

URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
07/10/2008				

Description :

In response to FDA request via email on July 2, 2008 regarding formulations used in clinical studies (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
07/08/2008				

Description :

Email correspondence providing a desk copy of Novartis ' response to FDA 's request for information on June 23, 2008 concerning the QT clinical studies (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
07/07/2008				

Description :

Email correspondence providing FDA with desk copy of Novartis ' response to the agency 's request of July 2, 2008; pertaining to RFI formulations (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
CMC
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
07/02/2008				

Description :

FDA email with attached fax request for further information on the formulation of Coartem used in the 8 Key clinical studies and the supportive studies for NDA 22-268 (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
07/02/2008				

Description :

Submission of additional CRFs specifying patient identification numbers , as requested by the agency of June 18, 2008 (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
07/02/2008				

Description :

Email correspondence providing gateway receipts for FDA's ECG subset data request of May 21, 2008 (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
07/02/2008				

Description :

FDA email containing fax request , seeking clarity on Novartis ' request for priority review (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
07/02/2008				

Description :

In response to FDA request of May 21, 2008; Novartis is providing QTc outlier analyses by treatment as well as separate analyses for patients with normal and elevated baseline QT /QTc intervals for each of the 8 key studies (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Information	Supplement Number
06/27/2008				

Description :

Email correspondence to FDA providing gateway receipts of drug product presubmission (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Request	Supplement Number
06/27/2008				

Description :

Email correspondence with FDA responding to email request for narratives and case report forms for all subjects who experienced serious or non -serious atrial fibrillation in ZOL 446H2301, ZOL446H2310. Novartis previously provided this information via SN 470 and SN488 (PS)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
06/27/2008				

Description :

Final pre-submission of rolling NDA , which comprises of Administrative Documents , Clinical Overview, the Summary of Biopharmaceutic Studies /Clinical Pharmacology Studies and the Proposed Labeling (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
CMC

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
06/26/2008				

Description :

Pre-submission of complete electronic drug product section , as well as the complete CMC Quality Overall Summary (Module 2 in the CTD format) for both drug substances and drug product (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Request	Supplement Number
06/23/2008				

Description :

FDA email with attached fax request for QT -Interdisciplinary Review (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
06/20/2008				

Description :

Email correspondence with the FDA advising on status of agency request , which is being followed -up by Basel (ES)

URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Memo of Record (telephone report)

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
06/20/2008				

Description :

Telecon with Gregory DiBernardo of FDA discussing status of Coartem NDA . Unlikely NDA approval before the end of September 2008. Potential Advisory Committee meeting being discussed by FDA team, but there's currently no confirmation of same (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Memo of Record (telephone report)

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
06/20/2008				

Description :

Telecon with FDA project manager advising that he will be sending a fax about the QTc data with questions for Novartis (PS)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
06/19/2008				

Description :

Submission to FDA requesting that the agency assigns Priority Review to the Coartem NDA priority (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
06/19/2008				

Description :

Email follow-up with FDA advising that the clinical team in Basel , Switzerland is preparing a response to your request for an update on the clinical site records (ES)

URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
06/19/2008				

Description :

Response to FDA request made via email by Gregory DiBernardo on June 4, 2008; requesting clarification of information for patient 0088 in Study CCOA 566A1023 (ESG)

URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
06/18/2008				

Description :

FDA email with attached fax requesting 10 % random sample of subject Case Report Forms for clinical study ABMO 2 (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
06/16/2008				

Description :

Response to FDA request for additional CRFs , specifying patient identification numbers , as received on June 4, 2008 for Study B2303 (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Information	Supplement Number
06/11/2008				

Description :

Follow-up email to FDA advising that applications for "artemether" and "lumefantrine" have been submitted (via e-mail) to Ms. Stephanie Shubat, Director, USAN (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Request	Supplement Number
06/11/2008				

Description :

Email correspondence with FDA responding to FDA's email query of June 4, 2008 for clarification of information on a CRF . Official response will be submitted to the NDA .
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Information	Supplement Number
06/11/2008				

Description :

FDA email advising that 10% random sample for AMD 02 will be faxed shortly and seeking follow -up information on the date of submission of USAN names (ES)

URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Information	Supplement Number
06/11/2008				

Description :

FDA email advising that the fax requesting the 10% random sample of subject Case Report Forms for study ABMO2, has been delayed pending comments from the team Lead Biostatistician (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Information	Supplement Number
06/11/2008				

Description :

Email correspondence with FDA advising that USAN applications were sent on June 11, 2008 (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type : Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
06/10/2008				

Description :

NDA presubmission of Human Pharmacology and Bioavailability /Bioequivalence Studies 2104, 2102, and 2302 (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Information	Supplement Number
06/10/2008				

Description :

Email correspondence with FDA advising that FDA email of June 10, 2008 was not received and querying as to whether gateway receipts were received (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Information	Supplement Number
06/10/2008				

Description :

Email correspondence to FDA providing gateway receipts for the last 3 of the 9 ClinPharm/PK studies with datasets , 2104, 2102, 2302 (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Information	Supplement Number
06/09/2008				

Description :

Email correspondence with FDA providing update on status for providing trade name appeal , priority review, response to FDA request for QTc data , CRF and patient taking dexamethasone (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
06/05/2008				

Description :

Submission of the last of the 8 key clinical studies with electronic datasets for study ABMO 2 (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
06/05/2008				

Description :

Email correspondence with FDA providing gateway receipts for final I key clinical study report (ABMO2) and providing a status on remaining pre-submissions
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Request	Supplement Number
06/04/2008				

Description :

FDA email with attached fax request for the 10% Random Sample of subject Case Report Forms for study B2303 (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
06/04/2008				

Description :

FDA email request seeking clarification on whether patient 0088 in study CCOA 566A1023, was prescribed two doses of dexamethasone (20mg IV x 2) or if the order was crossed out (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Information	Supplement Number
06/03/2008				

Description :

Email correspondence providing Gateway Receipts for submission of CP and PK stduies on June 3, 2008 (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
06/02/2008				

Description :

NDA Presubmission of NDA Bioanylitical methods report and Human PK and PD studies ; 2101, 020, 022, 024, and 027 (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
06/01/2008				

Description :

In response FDA request of June 10, 2008, made via email communication from the requesting an update on the 8 key study sites documentation (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No.	Manufactures Report Number:	FDA Letter Information	Supplement Number
05/30/2008				

Description :

Email correspondence providing FDA status of USAN name selection and advising that the target date for submitting the response to the April 25, 2008 trade name review is the end of the week of June 2, 2008 (PS)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
05/29/2008	2303			

Description :

Pre-submission of key clinical study report for study 2303 (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Information	Supplement Number
05/28/2008				

Description :

FDA email seeking a status on where Novartis is on establishing artemether and lumefantrine as USAN names. FDA also seeks to determine time line for receiving response to FDA comments of April 25, 2008 (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Information	Supplement Number
05/28/2008				

Description :

FDA email seeking a status on where Novartis is on establishing artemether and lumefantrine as USAN names. FDA also seeks to determine time line for receiving response to FDA comments of April 25, 2008 (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Request	Supplement Number
05/27/2008				

Description :

FDA fax requesting 10% sample CRFs related to Novartis ' May 22, 2008 submission of the CSR for study 2403 (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Information	Supplement Number
05/27/2008				

Description :

Email providing gateway receipts for May 22, 2008 submission of studies 2403 and 2301 (Please note error in Subject and message .; Study 2401 should be 2403) (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
05/23/2008				

Description :

Pre-submission in response to FDA request of May 16, 2008 for additional CRFs , specifying patient identification numbers ; related to study 2401 (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
05/22/2008				

Description :

Presubmission of Clinical Study Report Study 2403 and Clinical pharmacology report Study 2301 (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
05/22/2008				

Description :

Email denoting that study number should be 2401 as opposed to 2401 (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
05/16/2008				

Description :

Submission of additional CRFs , specifying patient identification numbers for Study 023 and Study 028; as requested by the agency
on May 2, 2008 (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
05/16/2008				

Description :

Email providing receipts for gateway submission made on May 16, 2008 which contains requested CRFs for studies 023 and 028 (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
05/15/2008				

Description :

Email providing FDA gateway receipts for the CMC Drug Substance section of the Coartem NDA 22-268 that was sent through the gateway on May 15, 2008 (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
05/14/2008				

Description :

Email correspondence advising that agency that they should expect to receive the DS portion of the CMC section of the NDA (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
05/09/2008				

Description :

Email providing electronic submission gateway receipts for the submission of the clinical study information, pertinent to the 8 key studies, send to FDA on May 9, 2008 (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
05/09/2008				

Description :

Email to FDA advising that the May 9, 2008 pre-submission comprised an inadvertent omission of the clinical pharmacology report for study 2401's from the hpbiotoc . Provided in the email is the location of the corresponding bookmark (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
05/09/2008				

Description :

In Response to FDA 's request of March 7, 2008 for information to assist FDA review team in assessing the sites to be inspected ; Novartis is providing list of investigator , site locations and enrollment for each of 8 key clinical studies (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Request	Supplement Number
05/02/2008				

Description :

FDA fax requesting additional 10% of subjects CRFs from studies 023 and 028. Clinical Study Reports for these studies were submitted on April 8 and March 19, respectively (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
04/22/2008				

Description :

Novartis email to FDA providing electronic submission gateway receipts of PK study 006, submitted to the agency on April 22, 2008 (ES)

URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
04/22/2008				

Description :

Pre-submission of Study 006, of the 9 clinical pharmacology and PK studies with datasets , which was agreed to by the agency in their response on February 7, 2008 (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
04/18/2008				

Description :

Email corresondence providing updates , advising that Novartis just sent a number of clinical and clinical pharmacology / PK reports to the NDA and corresponding receipts are appended . There are only 2 or 3 other reports for the clinical and biopharmaceutics sections of the NDA (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Memo of Record (telephone report)

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
04/18/2008				

Description :

Telecon with FDA to discuss FDA 's tradename review , Advisory committee decision by FDA and Ongoing rolling NDA (ES)

URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
04/11/2008				

Description :

Novartis email correspondence to FDA ,providing a Reviewer 's Aid; which is a conversion by optical character recognition of the originally scanned 028 and 023 study reports (ES)

URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
04/08/2008				

Description :

Submission of the fourth clinical study report Study 023. No CRFs are included because there were no deaths or serious adverse events in this study (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
04/08/2008				

Description :

Email correspondence to FDA providing receipts for submission of study 023, which was sent to the FDA on April 8, 2008 (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Information	Supplement Number
04/07/2008				

Description :

FDA voice message details of April 1 and 2, 2008 from Diana Willard , regarding trade name review and rolling NDA progress (ES)

URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
04/01/2008				

Description :

Email correspondece to the agency providing an update on the progress of Novartis ' ubmitting additional sections of the rolling NDA for Coartem (ES)

URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Request	Supplement Number
03/25/2008				

Description :

FDA email seeking to find out when the Clinical Overview (Section 2) would be ready for submission . Subsequent reponse from Novartis advising that the plan is to submit the Clinical Overview in June , due to ongoing activities (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Information	Supplement Number
03/25/2008				

Description :

FDA email acknowledging Novartis ' response to FDA query of February 29, 2008, regarding the submission of the Clinical Overview section (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
03/20/2008				

Description :

Submission of additional CRFs , pertaining to clinical study reports for 025 and 026, as requested by FDA on March 11, 2008 and March 12, 2008 respectively (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
03/19/2008				

Description :

Presubmission of a third comparative study , Study Report 028 (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Request	Supplement Number
03/18/2008				

Description :

FDA email requesting desk copies of Pharm /Tox, as the agency 's server containing this section crashed. Agency is requesting copies of the following repeat dose toxicity studies : Study 94- 6152 and Study 94- 6153 (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
03/09/2008				

Description :

Presubmission of the fifth of 8 key clinical studies with electronic datasets ; studies 2401 2407 (preliminary report of ongoing pregnancy registry) and 1012 (dose optimization study) (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Request	Supplement Number
03/07/2008				

Description :

FDA email requesting a list of investigators and location of their sites (including full address), and enrollment by site for each of the 8 key studies, in support of potential DSI inspections at these sites (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Information	Supplement Number
02/27/2008				

Description :

FDA email correspondence advising Novartis that the medical officers will not request the random sample of CRFs for Study 025 for approximately 2 to 3 weeks (ES) 10%

URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
02/27/2008				

Description :

Pre-submission to rolling NDA providing clinical study report for study 026 (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Clinical
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
02/27/2008				

Description :

Response to FDA request made via email from Diana Willard and Dr Regina Alivisatos dated February 15, 2008.A point-by-point response to all questions raised by the agency is provided (ES)

URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Request	Supplement Number
02/15/2008				

Description :

FDA email correspondence requesting pfd file of study 25 and seeking clarification as to grouping A _ AEV dataset (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Request	Supplement Number
02/15/2008				

Description :

Follow-up email correspondence from FDA requesting information on patient 21 from study 25 (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Request	Supplement Number
02/13/2008				

Description :

Email correspondence with FDA regarding the timing of submission for the Clin Parm section (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Information	Supplement Number
02/11/2008				

Description :

FDA email acknowledging Novartis updates and receipt of CD containing 'Protocols of 8 key studies'. Disc will be loaded onto the agency 's server for distribution to reviewers (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Request	Supplement Number
02/07/2008				

Description :

FDA letter providing comments and requests in response to Novartis ' January 28, 2008 E- mail regarding Case Report Forms (CRFs), the Division would like submitted to NDA 22- 268 for Coartem (PS)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Memo of Record (telephone report)

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
02/01/2008				

Description :

Telecon with Diana Willard of FDA to discuss NDA items , which included ; COARTEM trademark review, CRFs, Protocol Copies , Rolling CMC NDA and CP /PK datasets (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter Acknowledge	Supplement Number
01/31/2008				

Description :

FDA letter acknowledging Novartis ' response of January 28, 2008, to questions send via email on January 17, 2008 (ES)

URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
01/28/2008				

Description :

Novartis' response to FDA questions , posed via email on January 17, 2008 (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
01/28/2008				

Description :

Email correspondence to FDA providing questions concerning Novartis ' anticipation of the Division 's request for additional CRFs (other than those agreed to be provide for deaths and serious AEs .) (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
01/17/2008				

Description :

Email correspondence with FDA regarding proposed clinical overview for Coartem (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Memo of Record (telephone report)

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
01/16/2008				

Description :

Summary of telecon with FDA concerning the rolling NDA for Coartem tablets (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
01/14/2008				

Description :

Fast Track Designation granted for treatment of infections due to plasmodium falciparum or mixed infections including p . falciparum .
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
12/21/2007				

Description :

FDA correspondence granting eCTD waiver request submitted December 14, 2007.
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
12/14/2007				

Description :

eCTD waiver request containing exception to eCTD requirement for N 22-268 NDA (October 2007) based on Memoranda 6 and 30. (ES)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
11/26/2007				

Description :

Letter acknowledging fast track designation request for the treatment of malaria . Date of submission requesting step -wise submission of NDA : October 30, 2007; Date of receipt of submission requesting step -wise submission of NDA : November 2, 2007; Date of submission of fast track designation request : November 15, 2007; Date of receipt of submission for fast track designation : November 16, 2007.

URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Other

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
11/15/2007				

Description :

Request for fast track designation of Coartem specifically for the following indication : treatment of infections due to plasmodium falciparum or mixed infections including p . falciparum. (ESG)
URL:

Read Attachments

NOVARTIS

DRAIRS
NDA SUBMISSION RECORD

Basic Information

Reference Number	File Location	Trade Name	Compound Code
22-268		Coartem®/Riamet®	COA 566A

Historical Information

Submission Information

Submission Type :
Preclinical

Submission Date	Protocol No	Manufactures Report Number:	FDA Letter	Supplement Number
10/30/2007				

Description :

Initial pre-submission of the non-clinical data section of the NDA (ESG).
URL:

Read Attachments